## REMARKS

Claims 1-7 and 10-13 are pending. Claims 11-13 stand withdrawn. Claim 1 has been amended to restrict the claims, in view of the finality of the restriction requirement, to the elected subject matter, *i.e.*, compounds wherein R^1-R^2- is a bivalent radical of formula (a-3). Entry of the amendment is requested pursuant to MPEP 714.13 because the amendment places the application in condition for allowance or in better form for appeal.

Applicants acknowledge receipt of "Letter Regarding Restarting the Time Period for Reply Due to the Improper Loading of the Office Action" dated June 22, 2009. The Letter indicates that Office Actions having a notification date between June 5, 2009 and June 10, 2009, such as the present Office Action, will have the time period for reply restarted to commence on the notification date of the Letter, *i.e.*, June 22, 2009.

Rejection under 35 U.S.C. § 103

Claims 1-7 and 10 stand rejected under 35 U.S.C. § 103 as allegedly obvious over U.S. 6,544,997 (Bosmans) in view of Lima, supplemented with Supuran, Chavatte, or Penning, further in view of U.S. 4,186,135 (Thominet). The Applicants maintain that the claims are nonobvious over the cited art and request withdrawal of the rejection.

The Office has identified Compound 103, set forth at col. 43-44 in Bosmans, as the closest prior art:

Compound 103, Bosmans
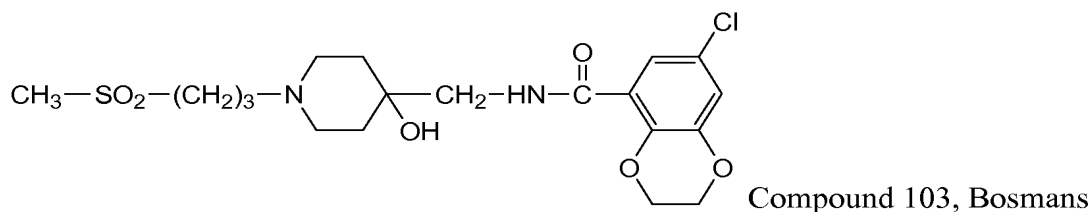
As acknowledged by the Office, among the differences between compound 103 and the claimed invention is the L substitutent. The claimed invention includes compounds wherein L is $-Alk-SO_2-NH_2$. Compound 103 of Bosmans has an $-Alk-SO_2-CH_3$ substitution. The Office alleges that the prior art teaches that $-SO_2-NH_2$ and $-SO_2-CH_3$ are "bioisosteric" and that one skilled in the art would have been motivated to replace the $-SO_2-CH_3$ of Bosmans with the $-SO_2-NH_2$ of the present invention.

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The Office's allegation that the "mere bioisosteric replacement with conventional conformational linkages is *prima facie* obvious" is misplaced – the Federal Circuit has never held that bioisosteric replacement is *prima facie* obvious. The Applicants note that the case cited by the Office, *Mead Johnson v. Premo Pharm.*, 207 USPQ 820, is a 1980 case from the District of New Jersey. As the Federal Circuit has recently opined on the legal issues cited in *Mead Johnson*, that case cannot be used to support any rejection made by the Office.

The law pertaining to obviousness as it applies to chemical compounds is clear: "An obviousness argument based on structural similarity between claimed and prior art compounds clearly depends on a preliminary finding that one of ordinary skill in the art would have selected the prior art compound as a lead compound." *The Procter & Gamble Co. v. Teva Pharmas. USA, Inc.*, 2009 U.S. App. LEXIS 10475, *7 (Fed. Cir. May 13, 2009) (a copy of which is attached hereto for the Office's convenience). The Office's allegation that compound 103 is a lead compound is based purely on hindsight. Table C.1 of Bosmans discloses 194 compounds, the great majority having the same or comparable activity as compound 103. While compound 103 was identified as active, there is no evidence that one would single out compound 103 as a compound meriting more investigation than any of the other compounds reported in Table C.1. Accordingly, the Office has failed to satisfy the Federal Circuit's requirement of first finding that compound 103 is a lead compound.

Nevertheless, even if the Office could establish that one skilled in the art would have selected compound 103 as a lead compound, the Office must establish "that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" and there must be "adequate support in the prior art for the change in structure." *Id.* at *10. Furthermore, the Office must demonstrate that a person of ordinary skill in the art would have had a "reasonable expectation of success" in synthesizing and testing the claimed compounds. *Id.* at *12-13. Accordingly, the Office's allegation that "modification of a lead compound with rational drug design using a bioisoteric replacement is *prima facie* obvious with expected variation in activity" finds no support in the law and is therefore insufficient to sustain a *prima facie* case of obviousness.

Moreover, "to the extent an art is unpredictable, as the chemical arts often are, [KSR v. Telefex's] focus on 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Id.* at *12. "[P]atents

are not barred just because it was obvious to explore a new technology or general approach that seemed to be a promising field of experimentation where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *Id.* at *14.

      The Office points to Supuran, Chavette and Penning to support that bioisosteric replacement of the sulfonamide is obvious. As the Applicants previously stated, Lima summarizes Penning. Specifically, Lima describes two cyclooxygenase-2 (COX-2) inhibitors prepared in Penning:
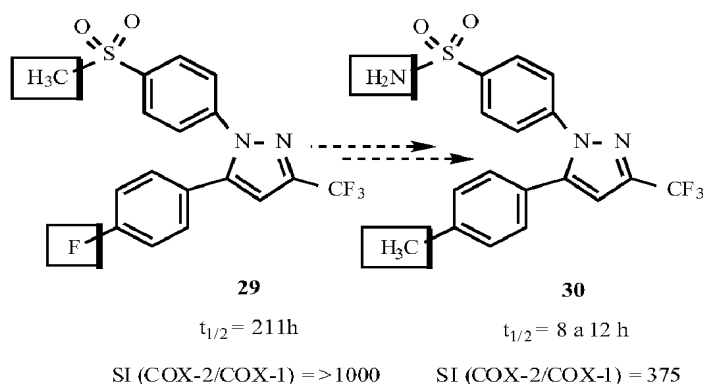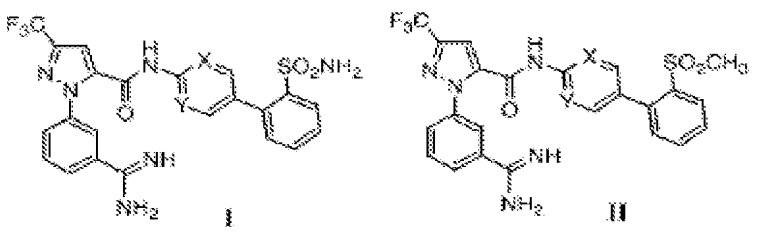

      As set forth in Lima, Compound 29, while very selective for COX-2 over COX-1 (SI COX-2/COX-1 > 1000), had a half life that was considered too long for the particular pharmaceutical use ($t_{1/2} - 211$ h). The $-SO_2-CH_3$ of Compound 29 was replaced with $-SO_2-NH_2$ to produce Compound 30. ***In addition, the fluorine of Compound 29 was replaced with $-CH_3$.*** Compound 30 ***is much less selective*** for COX-2 over COX-1 (SI COX-2/COX-1 = 375) ***and it has a significantly shorter half life*** ($t_{1/2} - 8$-12 h), as compared to Compound 29. Thus, "bioisosteric" replacement results in a compound ***having different pharmacological properties***. Moreover, the compounds of the claimed invention are structurally different from the compounds of Lima and are reported to act at a different receptor than those of Lima. The pending Office Action fails to properly acknowledge or account for these differences and the fluorine replacement in reaching its conclusion of obviousness.

      Supuran describes the following COX-2 inhibitor compounds, **5** and **6**:
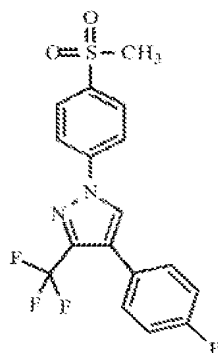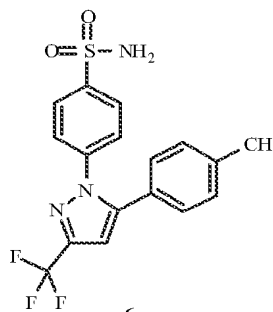
5 (SC 58125)   6   **6** (Celecoxib)

Supuran describes that the biological activities of **5** and **6** as to CA inhibition are different. *See* Supuran Table 1. Similar COX-2 inhibitors and activities are described in Chavatte. Thus, "bioisosteric" replacement results in a compound ***having different pharmacological properties***. Moreover, the compounds of the claimed invention are structurally different from the compounds of Supuran and Chavette and are reported to act at a different receptor than those of Supuran and Chavette. Again, the Office Action does not sufficiently account for these differences in reaching its conclusion of obviousness.

Supuran, Chavatte, and Penning describe replacement of sulfone by sulfonamide and teach that such a replacement leads to compounds having pharmacological activities that one skilled in the art could not have predicted. To further support the unpredictability of "bioisosteric" replacement, the Applicants direct the Office to Pinto, et al., *J. Med. Chem.* **2001**, *44*, 566-578, a copy of which is attached. Table 3, page 571, depicts in vitro activities of 3-trifluoromethylpyrazole compounds. As can be seen in Table 3 (set forth below), the sulfonamides (compounds of formula I) have different activities as compared to the sulfones (compounds of formula II). Compare compounds 14a and 14e and compounds 14d and 14f.

Table 3. In Vitro Activities Profile of P$_4$ Variants in the 3-Trifluoromethylpyrazole Series

compd	I/II	X	Y	human in vitro FXa[a] K_i, nM	human in vitro thrombin[a] K_i, nM	human in vitro trypsin[a] K_i, nM
2b		CH	CH	0.013	300	16
2k		C—F	CH	0.005	210	4.6
14a	I	CH	CH	0.015	40	3.9
14b	I	N	CH	0.009	400	50
14c	I	N	N	0.010	900	20
14d	I	C—F	CH	<0.005	120	4.0
14e	II	CH	CH	0.008	70	4.3
14f	II	C—F	CH	<0.005	50	3.4

^{a,b} Refer to Table 1.

As demonstrated by the cited art, "bioisosteric" replacement of functional groups in a molecule has an unpredictable effect on the biological activity of the resulting molecule and as a result, cannot be used to support a case of prima facie obviousness. Such findings and teachings are pertinent and support reconsideration and withdrawal of the rejections under § 103.

Obviousness-type double patenting

Claims 1-7 and 10 stand rejected under the doctrine of obviousness-type double patenting over U.S. Application Nos. 10/560,479; 10/560,485; and 10/560,486 in view of Lima supplemented with Supuran, Chavette, or Penning. In view of the foregoing comments regarding the cited art, the Applicants assert that the rejection is improper and request its withdrawal.

Conclusion

The Applicants assert that the foregoing constitutes a full and complete reply to the June 9, 2009 Office Action and that claims 1-7 and 10 are in condition for allowance. An early notice to that effect is, therefore, earnestly solicited.

Date: August 19, 2009   /Stephanie A. Barbosa/

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Discovery of 1-[3-(Aminomethyl)phenyl]-N-[3-fluoro-2-(methylsulfonyl)-[1,1'-biphenyl]-4-yl]-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (DPC423), a Highly Potent, Selective, and Orally Bioavailable Inhibitor of Blood Coagulation Factor Xa[1]

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Factor Xa (fXa) plays a critical role in the coagulation cascade, serving as the point of convergence of the intrinsic and extrinsic pathways. Together with nonenzymatic cofactor Va and Ca^{2+} on the phospholipid surface of platelets or endothelial cells, factor Xa forms the prothrombinase complex, which is responsible for the proteolysis of prothrombin to catalytically active thrombin. Thrombin, in turn, catalyzes the cleavage of fibrinogen to fibrin, thus initiating a process that ultimately leads to clot formation. Recently, we reported on a series of isoxazoline and isoxazole monobasic noncovalent inhibitors of factor Xa which show good potency in animal models of thrombosis. In this paper, we wish to report on the optimization of the heterocyclic core, which ultimately led to the discovery of a novel pyrazole SN429 (**2b**; fXa K_i = 13 pM). We also report on our efforts to improve the oral bioavailability and pharmacokinetic profile of this series while maintaining subnanomolar potency and in vitro selectivity. This was achieved by replacing the highly basic benzamidine P_1 with a less basic benzylamine moiety. Further optimization of the pyrazole core substitution and the biphenyl P_4 culminated in the discovery of DPC423 (**17h**), a highly potent, selective, and orally active factor Xa inhibitor which was chosen for clinical development.

Introduction

Anticoagulants currently available for the treatment and prevention of thromboembolic diseases include warfarin (Coumadin), heparins, hirudin, hirulog, and argatroban.[2–7] Coumadin, a vitamin K-dependent inhibitor, has a slow onset, high oral efficacy, and long duration of action. Heparins and direct thrombin inhibitors have a rapid onset of action, but they must be administered parenterally. The normal protocol for patients on these therapies requires careful monitoring of clotting times to achieve efficacy and dose titration to minimize excessive bleeding.[5] Therefore, there is a serious effort to identify orally active anticoagulants that are clinically safe and which require less monitoring.

Factor Xa (fXa), a trypsin-like serine protease, holds the central position that links the intrinsic and extrinsic mechanisms in the blood coagulation cascade.[8] The physiological role of activated fXa is to proteolytically activate thrombin.[9] Thrombin has several procoagulant functions that include the activation of platelets, the feedback activation of other coagulation factors, and the conversion of fibrinogen to insoluble fibrin clots. Small molecule thrombin inhibitors have been intensely investigated.[10] More recently, direct inhibition of fXa has emerged as an attractive strategy for the discovery of novel antithrombotic agents.[10,11] Since fXa inhibitors

specifically affect coagulation, but not platelet function, this mechanism may be anticipated to have less potential to increase the risk of abnormal bleeding relative to thrombin inhibitors and antiplatelet agents. A comparison between hirudin (a thrombin inhibitor) and tick anticoagulant peptide (TAP, an fXa inhibitor) suggests that inhibition of fXa may result in less bleeding risk, leading to a more favorable safety/efficacy ratio.[12]

Several potent monobasic inhibitors of fXa have been published (from our laboratories as well as by others).[13] Our efforts have recently led to the discovery of potent isoxazoline analogues such as SF303[14] and, more recently, include potent isoxazoles such as SA862 (**1**, fXa K_i = 0.15 nM, Figure 1).[15] The lack of chirality of the isoxazole and its high affinity for fXa made it an attractive template for further optimization. In this paper, we wish to discuss the SAR of other five-membered heterocyclic templates in which the point of attachment to the P1 substituent is through a nitrogen atom on the heterocycle.

Chemistry

The synthesis of the 3-unsubstituted pyrazole **2a**, a compound chosen to best mimic the isoxazole core, was accomplished quite readily starting with the condensation of 3-cyanophenylhydrazine and 4-(dimethylamino)-2-oxo-but-3-enoic acid ethyl ester in acetic acid (Scheme 1).[16] The condensation afforded a 1:1 regioisomeric mixture of 3- and 5-substituted pyrazole esters. The desired pyrazole ester **4a** was obtained following puri-

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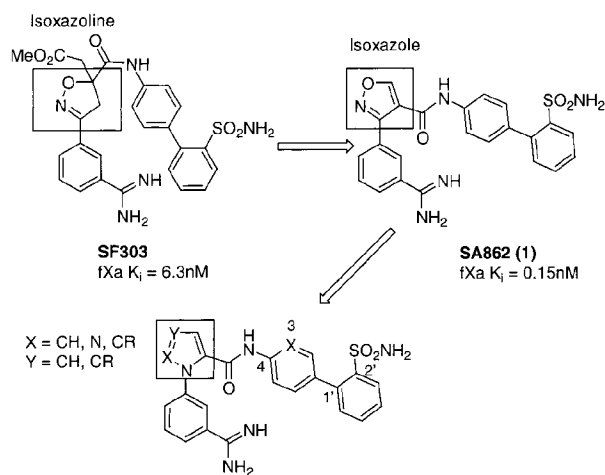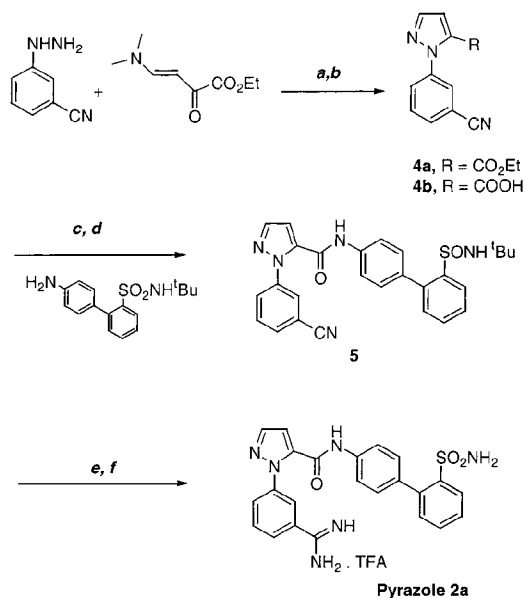
Figure 1. Optimization of the five-membered heterocyclic template.

Scheme 1. Synthesis of Pyrazole **2a**[a]

[a] (*a*) AcOH reflux, 17%; (*b*) LiOH/THF/water, 98%; (*c*) oxalyl chloride/CH₂Cl₂; (*d*) DMAP/CH₂Cl₂, 76%; (*e*) HCl, MeOH; (*f*) ammonia/MeOH, 45%.

fication via flash chromatography. Hydrolysis of the ester under basic conditions (LiOH/THF/water) gave the requisite pyrazole carboxylic acid derivative **4b**, which was treated with oxalyl chloride to form the acid chloride. This was then coupled with 4-amino[1,1-biphenyl]-2-*tert*-butylsulfonamide[14a] to provide the key intermediate **5**. Treatment of **5** under the Pinner conditions[14,15] (HCl/MeOH) afforded the imidate which was immediately reacted with excess ammonia in methanol to afford pyrazole analogue **2a** in moderate yield. The *tert*-butylsulfonamide substituent is simultaneously deprotected to the primary sulfonamide under these conditions.

The synthesis of a 3-substituted pyrazole **2b** is outlined in Scheme 2. Condensation of 3-cyanophenyl-hydrazine with methyl 2-methoxyimino-4-oxopentanoate afforded pyrazole **6** regioselectively.[17] Hydrolysis of **6** under basic conditions (LiOH/THF/water) gave the requisite carboxylic acid **6a** in good yield. This was then

Scheme 2. Synthesis of 3-Methyl Pyrazole Analogue **2b**[a]
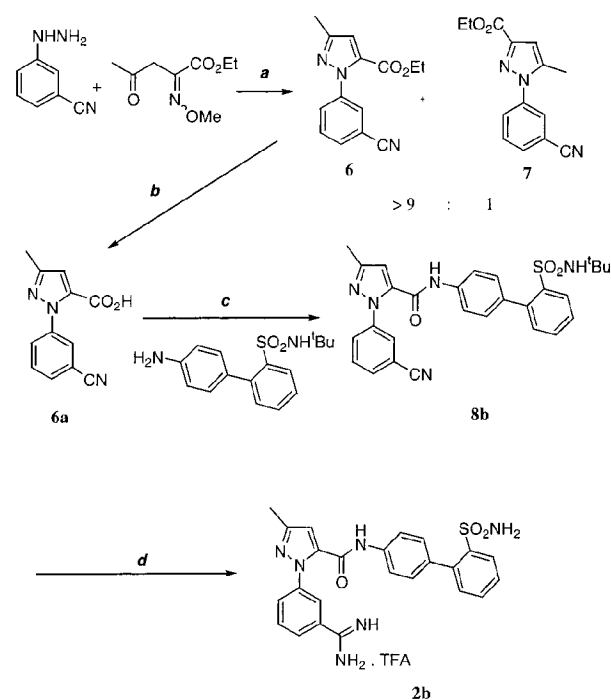
[a] (*a*) Acetic acid reflux, 75%, separated via flash chromatography; (*b*) LiOH/THF/H₂O, 90%; (*c*) oxalyl chloride/CH₂Cl₂ rt; DMAP/CH₂Cl₂/rt, 99%; (*d*) HCl/MeOH/ammonium carbonate/MeOH, TFA 80 °C, 36%.

coupled to 4-amino[1,1-biphenyl]-2-*tert*-butylsulfon-amide via the intermediate acid chloride (oxalyl chloride/DMAP, dichloromethane) to afford **8**. Alternatively, the ester **6** can be coupled with 4-amino[1,1-biphenyl]-2-*tert*-butylsulfonamide using the Weinreb trimethyl-aluminum[18] methodology to afford intermediate **8b** in good yield. Most of the amide P₄ variants, the 3-*n*-butyl analogue **2c**, and the *N*-methylated amide analogue **2d** were also prepared via the methodology outlined for **2b**. The desired benzamidine pyrazole analogues **2b**–**n** were obtained from the corresponding benzonitrile precursors via the Pinner amidine protocol described previously.

The synthesis of the trifluoromethylpyrazole analogue **14a** is outlined in Scheme 3. Condensation of *m*-bromo-phenylhydrazine with commercially available 1,1,1-trifluoro-2,4-pentanedione (Aldrich) afforded an insepa-rable regioisomeric mixture (8:2) of pyrazoles **9a** and **9b**. Treatment of **9a** and **9b** with copper cyanide in *N*-methyl pyrrolidinone at reflux provided cyanophenyl pyrazole intermediates **10a** and **10b**. Treatment of this mixture with NBS in refluxing carbon tetrachloride afforded the alkylhalides which were immediately con-verted to the hydroxymethyl intermediates **11a** and **11b** under basic conditions. At this stage the desired pyr-azole intermediate **11a** was easily separated and puri-fied via flash chromatography. Oxidation of **11a** with a mixture of ruthenium trichloride and sodium periodate then afforded the desired 3-trifluoromethylpyrazole-5-carboxylic acid intermediate **12**. Acid chloride coupling of **12** to 4-amino[1,1-biphenyl]-2-*tert*-butylsulfonamide provided benzonitrile precursor **13a**, which was treated under the Pinner amidine protocol to afford the desired benzamidine analogue **14a**. Trifluoromethylpyrazole analogues **14b**–**f** were prepared in a similar manner.

Scheme 3. Synthesis of 3-Trifluoromethylpyrazole Analogue **14a**
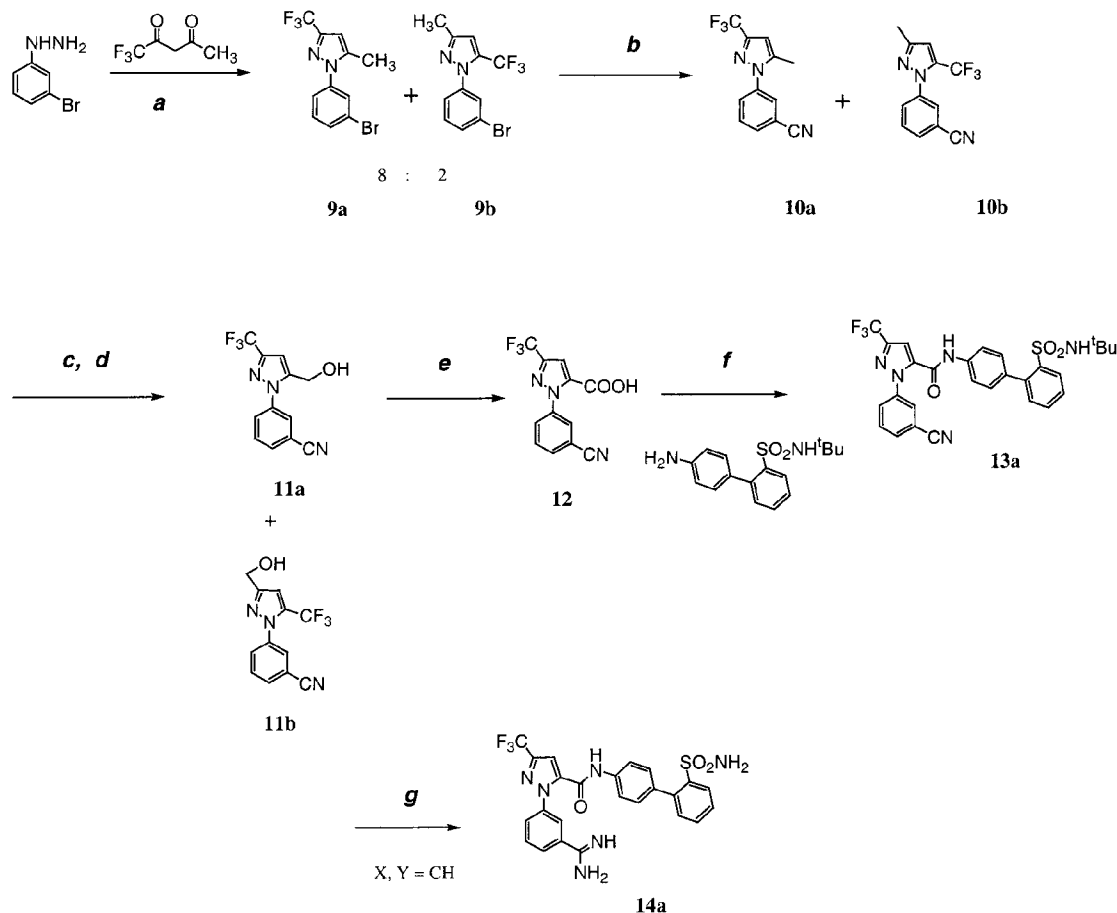
^{a} (**a**) AcOH/reflux/quant; (**b**) CuCN/NMP, reflux, 40%; (**c**) NBS/CCl$_4$, quant; (**d**) CaCO$_3$/dioxane/water, 44%; (**e**) NaIO$_4$/RuCl$_3$/CH$_3$CN/H$_2$O, 90%; (**f**) oxalyl chloride/CH$_2$Cl$_2$, quant; DMAP/CH$_2$Cl$_2$, 58%; (**g**) MeOH/HCl, ammonium carbonate/MeOH, TFA, 80 °C, 46%.

The synthesis of the pyrrole analogues **3a** and **3b** is shown in Scheme 4. Condensation of 3-aminobenzonitrile with 2,5-dimethoxytetrahydrofuran afforded the pyrrole intermediate **15a**.[24] Pyrrole **15a** was formylated (POCl$_3$/DMF) regioselectively at the 2-position to derivative **15b** which was then oxidized (potassium permanganate/acetone/water) to afford the desired carboxylic acid **15c** in good yield. To prepare the 3-bromopyrrole intermediate **15d**, the 2-formyl intermediate **15b** was first brominated regioselectively at the 3-position with NBS and then oxidized to the carboxylic acid as described above. Acid chloride coupling of either **15c** or **15d** with 4-amino[1,1-biphenyl]-2-*tert*-butylsulfonamide afforded intermediates **16a** and **16b** which after the Pinner reactions provided pyrrole analogues **3a,b**.

The benzonitrile precursors obtained as per Scheme 2 or 3 were subjected to reduction in a methanol-acetic acid medium using a Parr Shaker apparatus with catalytic palladium on carbon (5%) at 40 psi to afford benzylamine analogues **17a−h** (Scheme 5). Deprotection of the *tert*-butylsulfonamide protecting group with trifluoroacetic acid at 80 °C for 15 min afforded the requisite primary benzylamine analogue **17a**. Derivatives not containing a sulfonamide functionality were purified directly after reduction with palladium. Compound **17h** was dissolved in absolute methanol, and dry HCl gas was bubbled through the mixture for 15 min. DPC423 was obtained from this mixture by precipitation

with diethyl ether followed by recrystallization with methanol and ethyl acetate. Alternatively, **17h** was neutralized with aqueous sodium hydroxide (1 N) and subjected to the methodology described above to obtain DPC423.

Results and Discussion

Based on modeling experiments,[19] a pyrazole template was chosen to mimic the isoxazole core in compound **1**. Figure 2 shows an overlap of pyrazole **2a** with isoxazole **1** in the fXa active site. Pyrazole **2a** with a fXa K_i of 0.16 nM is equipotent to isoxazole **1** (fXa K_i = 0.15 nM). On the basis of these data, it appears that the isoxazole oxygen atom does not offer any binding advantages. Additionally, pyrazole **2a** offers the potential of substitution at the 3-position, which is not possible with the isoxazole core.

The 3-methylpyrazole analogue **2b** is an order of magnitude more potent than pyrazole **2a** (fXa K_i = 13 pM compared to 0.16 nM). Furthermore, the potency of **2b** compares favorably to the very potent and naturally occurring tick anticoagulant protein (TAP, fXa K_i = 100 pM).[20] Compound **2b** shows >1000-fold selectivity for fXa compared to thrombin and trypsin (Table 1). The X-ray structure of pyrazole **2b** complexed to bovine trypsin was determined (Figure 3).[21−23] The structure has been refined to a crystallographic R-factor of 19.2% at 1.80 Å resolution. As expected, the benzamidine P$_1$

Scheme 4. Synthesis of Pyrrole Analogues **3a** and **3b**[a]

15a R = H
15b, R = CHO
15c, R = COOH
15d

16a, R = H
16b, R = Br

R = H, **3a**

R = Br, **3b**
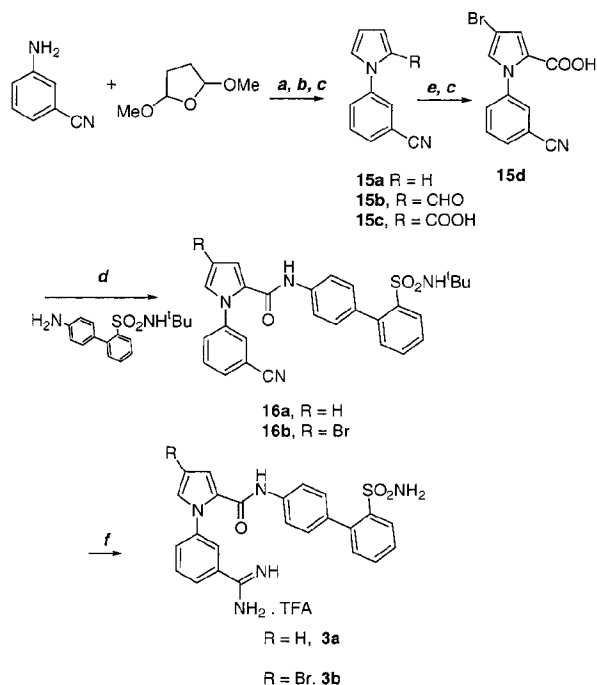
[a] (**a**) AcOH reflux, 93%; (**b**) DMF/POCl₃, 0 °C—reflux, 83%; (**c**) KMnO₄, acetone/water, 74%; (**d**) oxalyl chloride, quant, DMAP/CH₂Cl₂, 80%; (**e**) NBS/THF, rt, 53%; (**f**) HCl/MeOH, ammonium carbonate/MeOH, 60%; TFA, 80 °C, 70%.

forms a bidentate interaction with Asp-189 (2.9 Å and 3.0 Å in the S₁ specificity pocket). The dihedral angle between the pyrazole and the benzamidine P₁ substituent is 70°, which enables the pyrazole N-2 nitrogen to interact with the backbone NH of Gln-192 (3.2 Å) and form a Van der Waal interaction with Cys-220 (3.3 Å). The 3-methyl substituent on the pyrazole is near the solvent accessible surface at the outer ridge of the active site and within contact distance of Gly-218 and Cys-220. The amide carbonyl oxygen interacts with the NH of Gly-216 (3.2 Å) and also with Ser-214 (3.0 Å) through a bridging water molecule. Similarly, the amide NH
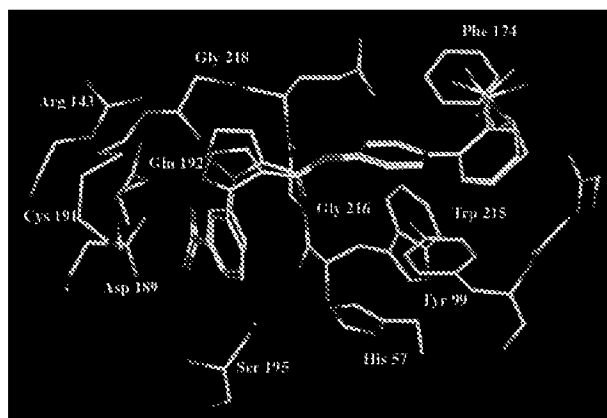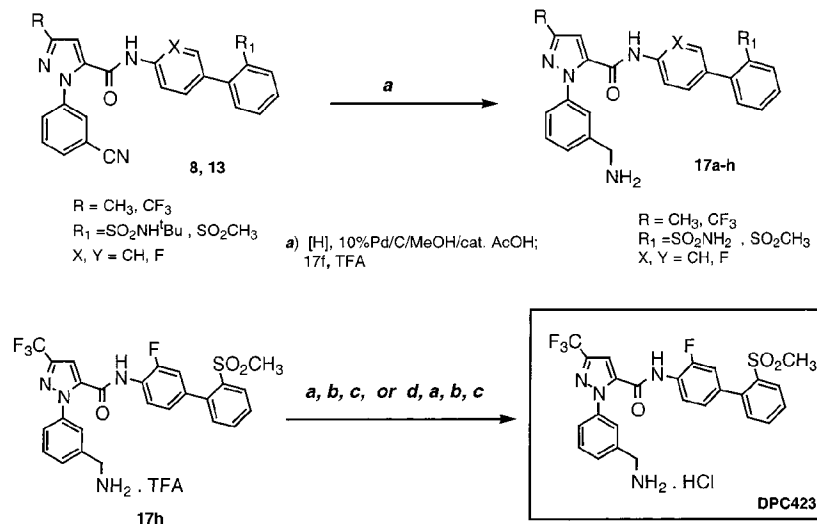

**Figure 2.** Overlay of pyrazole **2a** and SA862 in factor Xa.

interacts with Gly-218 (3.1 Å) through a bridging water molecule. The P₄ *o*-biphenylsulfonamide substituent is situated in the S₄ region with the terminal phenyl-sulfonamide ring forming an edge to face interaction with Trp-215. Overall, the conformations adopted by the trypsin bound inhibitor and that predicted by the binding of pyrazole analogue **2a** in the active site of fXa are similar.

To address the importance of substitution on the core template, we examined the fXa activity of pyrrole analogues **3a** and **3b**. The 5-fold loss in fXa potency for pyrrole analogue **3a** compared to pyrazole **2a** confirms that the N-2 nitrogen in the pyrazole ring is indeed important for potency. The 3-bromo pyrrole **3b** analogue while more potent than **3a** is still significantly less potent than the 3-alkyl substituted pyrazoles **2b** and **2c**.

The N-methylation of the central amide linker as in **2d** resulted in >800-fold loss of factor Xa potency compared to the secondary amide analogue **2b**. It is possible that the loss in fXa activity is due to a change in the amide bond conformation brought about by the *N*-methyl substitution. Further work is currently being pursued to determine the importance of the amide NH and will be reported in due course.

Scheme 5. Synthesis of Benzylamine P₁ Analogues

8, 13

R = CH₃, CF₃
R₁ =SO₂NH'Bu , SO₂CH₃
X, Y = CH, F

a) [H], 10%Pd/C/MeOH/cat. AcOH; 17f, TFA

17a-h

R = CH₃, CF₃
R₁ =SO₂NH₂ , SO₂CH₃
X, Y = CH, F

17h

a, b, c, or d, a, b, c

DPC423

[a] (**a**) MeOH, 0 °C, HCl(gas) 0.15 min; (**b**) diethyl ether; (**c**) recrystallized, MeOH/EtOAc or (**d**) neutralize, NaOH (1 N).

Table 1. Comparison of SA862 with Pyrazole and Pyrrole Analogues

SA862

Pyrazoles 2a-d

Pyrroles 3a,b
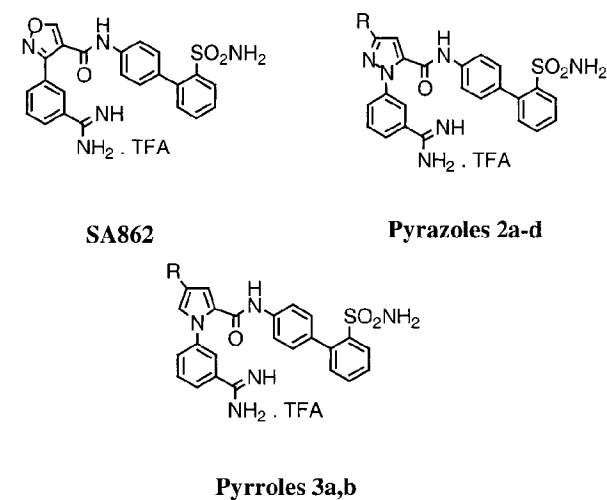
compd[b]	R	human in vitro FXa[a] K_i, nM	human in vitro thrombin[a] K_i, nM	human in vitro trypsin[a] K_i, nM
isoxazole				
SA862 (1)		0.15	2800	21
pyrazoles				
2a	H	0.16	900	15
SN429 (2b)	Me	0.013	300	16
2c	n-Bu	0.06	300	11
2d N-Me amide	Me	11.00	>2000	>1600
pyrroles				
3a	H	0.80	900	56
3b	Br	0.29	300	32

[a] Human purified enzymes were used. K_i values are averaged from multiple determinations ($n = 2$), and the standard deviations are <30% of the mean. K_i's were measured as in ref 14a,b. [b] All compounds gave satisfactory analytical data (C, H, N; ±0.4% of theoretical values).
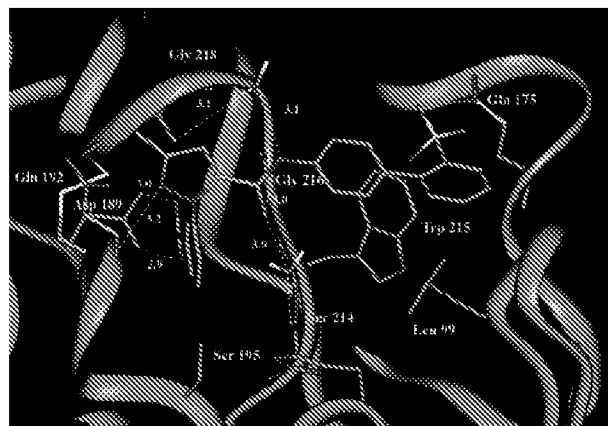
Figure 3. X-ray structure of pyrazole **2b** in bovine trypsin.

P₄ Modifications. In the isoxazoline series,[14] the *o*-biphenylsulfonamide moiety and the corresponding *o*-biphenylmethylsulfone were identified as optimal P₄ substituents. The potent fXa binding activity shown for these compounds is due to the highly constrained orientation, in which the P₁ benzamidine and the P₄ biphenylsulfonamide substituents are in a 1,3-relationship on the isoxazoline core. In these examples, the terminal phenyl ring of the 2'-biphenylsulfonamide P₄
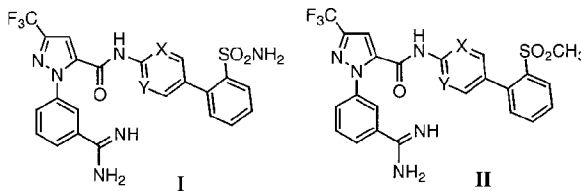
Table 2. In Vitro Activity Profile of P₄ Variants in the 3-Methylpyrazole Series

compd	X	Y	R	human in vitro FXa[a] K_i, nM	human in vitro thrombin[a] K_i, nM	human in vitro trypsin[a] K_i, nM
2b	CH	CH	SO₂NH₂	0.013	300	16
2e	CH	CH	SO₂CH₃	0.008	180	13
2f	CH	CH	CF₃	0.040	300	49
2g	CH	CH	F	0.460	450	100
2h	CH	CH	H	1.300	600	87
2i	N	CH	SO₂NH₂	0.007	1400	59
2j	N	N	SO₂NH₂	0.041	7400	150
2k	C−F	CH	SO₂NH₂	0.005	210	4.6
2l	C−Br	CH	SO₂NH₂	0.010	200	17
2m	C−Cl	CH	SO₂NH₂	0.009	300	15
2n	C−F	CH	SO₂CH₃	0.020	230	

[a,b] Refer to Table 1.

is orthogonal to the inner phenyl ring, forming an edge-to-face interaction with Trp-215. This orthogonal arrangement places the sulfonamide or the sulfone substituent in close proximity to the OH group of Tyr-99. In the case of the isoxazole and pyrazole series, the P₁ and the P₄ substituents are 1,2-substituted on the heterocycle. The rigid framework adopted by these inhibitors are complementary to the fXa active site and places the P₄ substituent in a highly optimized fashion in the S₄ region. Table 2 summarizes the fXa activity of additional substituted P₄ biaryl, pyridylphenyl, and pyrimidylphenyl pyrazole analogues. In the biaryl series, the order of potency for the 2'-substituted biphenyl P₄ substituents is SO₂CH₃ ≥ SO₂NH₂ > CF₃ > H. While the rank order of potency for these compounds is similar to that previously determined for the isoxazoline series,[14] the pyrazoles are significantly more potent. Substitution at the 3-biphenyl position (proximal phenyl) was clearly shown to affect the potency of the isoxazoline and isoxazole analogues. In the pyrazole series, the introduction of a 3-fluoro (**2k**) substituent on the proximal phenyl ring or the replacement of this ring with a 2-pyridyl ring (**2i**) results in a 2−3-fold enhancement in potency. In general, the 3-halogen biphenyl substituents improve potency in the order of F > Cl ≥ Br > H. The pyrimidyl analogue (**2j**) shows a slight loss in activity when compared to **2b** or **2i**, but it is still considerably more potent than pyrazole **2a**. The substituted biaryl analogues show good selectivity for fXa compared to thrombin but are less selective over trypsin. However, improved trypsin selectivity is observed for the aza P₄ analogues **2i** and **2j**. Thus, in the 3-methylpyrazole series, the combination of either a 3-fluoro substitution on the proximal phenyl ring or the 3-pyridyl substitution, with either an *o*-methylsulfone or *o*-sulfonamide substituent on the terminal P₄ phenyl ring, is considered optimal for potency or selectivity or both.

Substitution on Pyrazole Core. The replacement of the 3-methyl substituent with a longer substituent, such as butyl analogue **2c** (Table 1), results in a 2-fold loss in potency, albeit still 3-fold more potent than the

Table 3. In Vitro Activities Profile of P_4 Variants in the 3-Trifluoromethylpyrazole Series

| compd	I/II	X	Y	human in vitro FXa[a] K_i, nM	human in vitro thrombin[a] K_i, nM	human in vitro trypsin[a] K_i, nM
2b		CH	CH	0.013	300	16
2k		C–F	CH	0.005	210	4.6
14a	I	CH	CH	0.015	40	3.9
14b	I	N	CH	0.009	400	59
14c	I	N	N	0.010	900	20
14d	I	C–F	CH	<0.005	120	4.0
14e	II	CH	CH	0.008	70	4.3
14f	II	C–F	CH	<0.005	50	3.4

[a],[b] Refer to Table 1.

Table 4. Dog Pharmacokinetics and Antithrombotic Efficacy of Benzamidine Analogues

compd	Cl (L/kg/h)[a]	V_{dss} (L/kg)[a]	$t_{1/2}$ (h)[a]	F% (po)[b]	Caco-2[c] $P_{app} \times 10^{-6}$ cm/s	rabbit A-V shunt[d] ID$_{50}$ (μmol/kg/h)
2b	0.67	0.29	0.82	4	0.30	0.02
2f	0.47	0.47	3.72	NT	NT	0.24
2i	0.76	0.21	0.31	<1	NT	0.07
2j	0.36	0.20	3.32	<5	NT	0.03
14c	0.33	0.25	1.40	NT	0.10	NT
14f	1.10	3.80	3.80	0	0.20	NT

[a] Dose of 1 mg/kg IV. [b] Oral dose of 4 mg/kg. [c] Reference 27. [d] Reference 26.

unsubstituted pyrazole **2a**. Since the methyl analogue **2b** shows much better potency than the longer chain alkyl substitutions, the 3-trifluoromethyl pyrazole was prepared. Although it was anticipated that the trifluoromethyl substituent would exhibit a better hydrophobic interaction with the fXa enzyme than the 3-methyl substituent, the 3-trifluoromethylpyrazole *o*-biphenyl-sulfonamide P_4 analogue **14a** (Table 3) and the corresponding 3-methylpyrazole analogue **2b** were found to have similar potency. Comparable potencies were also observed for the respective pyridyl analogues **14b** and **2i**. However, in the pyrimidyl series, a 4-fold improvement was observed for the trifluoromethyl pyrimidyl analogue **14c** compared to the corresponding methyl analogue **2j**. A similar enhancement was also observed for the 3-fluoro analogue **14d**. The methylsulfonyl analogue **14e** was 2-fold more potent than the corresponding sulfonamide **14a**, and as anticipated, a further increase in affinity was observed with the 3-fluoro analogue **14f**. Compounds **14d** and **14f** clearly suggest that the 3-trifluoromethyl substituent, when taken together with an optimized biaryl P_4 moiety, results in extremely high affinity molecules. These two compounds are currently the most potent fXa inhibitors reported in the literature to date.
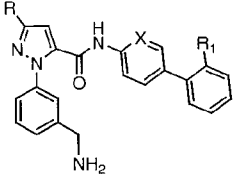
In Vivo Profile of Benzamidine Analogues. The pharmacokinetic profiles for a select set of benzamidine analogues were determined (Table 4). When dosed intravenously in beagle dogs, the biaryl P_4 analogues **2f** and **2i** have relatively low clearance and moderate
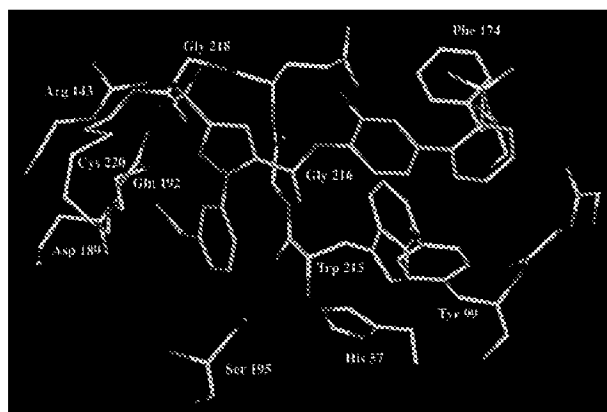
Figure 4. Binding model of pyrazole **17h** in factor Xa.

half-lives ranging from 0.3 to 3.7 h. The pyrimidyl P_4 analogues **2j** and **14c** show lower clearance than the other compounds evaluated but still show moderate duration of action due to their relatively low volume of distribution. The analogue **14f** has slightly higher clearance than the other compounds in this set, but it also has a higher volume of distribution and longer half-life (3.8 h). When administered orally, these benzamidine analogues show poor oral bioavailability (<5%). The poor permeability is likely a result of the highly charged amidine functionality ($pK_a \sim 10.7$), which was predicted based on the low Caco-2 permeability coefficient P_{app} values obtained for these compounds.

The antithrombotic efficacy of a number of benzamidine analogues was evaluated in a rabbit arterio-venous shunt thrombosis model (Table 4).[26] These compounds were administered by intravenous infusion, and the antithrombotic effect was measured as the ID$_{50}$ (dose which reduced clot weight by 50%). In this assay, pyrazole analogues **2b**, **2f**, **2i**, and **2j** inhibit thrombus formation in a dose dependent manner with ID$_{50}$'s ranging from 0.23 μmol/kg/h to 0.02 μmol/kg/h.
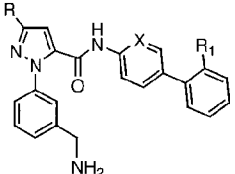
Benzylamine P1 Analogues. To improve the oral absorption of the pyrazole analogues, we adopted a strategy of replacing the P_1 benzamidine with a less basic moiety (preferably with $pK_a < 10$). One of the first benzamidine replacements considered was the benzyl-amine moiety (pK_a of ~8.8). We modeled the benzyl-amine analogue **17h** in the active site of fXa (Figure 4) and determined that the conformation assumed by **17h** was very similar to that seen for benzamidine **2b**. In the case of the benzylamine analogue **17h**, the single amino functionality interacts with Asp-189, but is not capable of a bidentate interaction such as that seen for the benzamidine analogue **2b**. In addition, since no interaction is observed with Ser-190, some loss in fXa activity was expected. Since the pyrazole series was optimized to the 5–10 pM range, we were able to sacrifice up to 2 orders of magnitude in potency in exchange for compounds with improved oral absorption. The in vitro data for the benzylamine analogues **17a–d** is reported in Table 5. A quick review of the data shows similar fXa potency trends as seen in the benzamidine series. The benzylamine analogue **17a** (fXa $K_i = 2.5$ nM) is 190-fold less potent than its benzamidine counterpart **2a** (fXa $K_i = 0.013$ nM). The incorporation of a 3-F substituent in the proximal phenyl ring resulted in **17b** with a modest improvement in potency (fXa $K_i = 1.6$

Table 5. Profile of Pyrazole Benzylamine P_1 Analogues

compd	R	X	R_1	human in vitro FXa[a] K_i, nM	human in vitro thrombin[a] K_i, nM	human in vitro trypsin[a] K_i, nM	rabbit A-V shunt[b] ID_{50} (μmol/kg/h)	human APTT, μM	HPB[c]
2b (amidine)	CH_3	CH	SO_2NH_2	0.013 (0.03)[d]	300	16	0.02	0.44	70
17a	CH_3	CH	SO_2NH_2	2.70 (4.10)[d]	21000	250	NT	2.30	63
17b	CH_3	C–F	SO_2NH_2	1.60 (2.20)[d]	12000	120	NT	0.92	70
17c	CH_3	CH	SO_2CH_3	0.89	21000	220	NT	1.30	NT
17d	CH_3	C–F	SO_2CH_3	0.48 (1.20)[d]	14000	130	0.90	1.10	75
17f (amidine)	CF_3	C–F	SO_2CH_3	<0.005	50	3.4	NT		NT
17e	CF_3	CH	SO_2NH_2	0.91 (2.10)[d]	14000	120	1.00	6.40	83
17f	CF_3	C–F	SO_2NH_2	0.36 (1.00)[d]	2000	53	0.60	0.91	93
17g	CF_3	CH	SO_2CH_3	0.38	5800	100	2.20	2.20	77
17h	CF_3	C–F	SO_2CH_3	0.15 (0.30)[d]	6000	60	1.10 (0.15)[e]	4.86	89

[a] Refer to Table 1. [b] Reference 26. [c] HPB refers to human protein binding; all compounds gave satisfactory analytical data including C, H, N within ± of theoretical values. [d] Rabbit in vitro data. [e] IC_{50}, which is the concentration to inhibit thrombus formation by 50% in rabbits.

Table 6. Dog Pharmacokinetic Profile of Benzylamine Analogues

compd	X	R_1	Cl (L/kg/h)	V_{dss} (L/kg)	$t_{1/2}$ (h)	F% (po)	Caco-2[a] $P_{app} \times 10^{-6}$ (cm/s)
			R = CH_3				
2b (amidine)	CH	SO_2NH_2	0.67	0.29	0.82	4.40	0.30 ± 0.07
17a	CH	SO_2NH_2	0.43	1.90	9.30	13	0.20 ± 0.03
17b	C–F	SO_2NH_2	0.30	0.60	2.80	10	0.95 ± 0.02
17c	CH	SO_2CH_3	0.98	3.62	5.80		1.20 ± 0.09
17d	C–F	SO_2CH_3	2.10	3.10	1.90	73	3.14 ± 0.10
			R = CF_3				
14f (amidine)	C–F	SO_2CH_3	1.10	3.80	3.80	<1	0.20 ± 0.01
17e	CH	SO_2NH_2	0.75	4.36	7.88	35	bql
17f	C–F	SO_2NH_2	0.10	0.34	4.70	22	0.91 ± 0.11
17g	CH	SO_2CH_3	0.44	5.82	9.50	39	3.38 ± 0.08
17h	C–F	SO_2CH_3	0.24	0.90	7.50	57	4.86 ± 0.33

[a] IV dose = 0.5 mg/kg. [b] Oral dose = 0.2 mg/kg. [c] Reference 27.

nM) and improved permeability in the Caco-2 assay with a P_{app} value of 0.95×10^{-6} cm/s compared to 0.2×10^{-6} cm/s (Table 6). Replacing the 2-sulfonamide on the terminal phenyl ring with the 2-sulfonylmethyl substituent afforded **17c** (fXa K_i = 0.89 nM). This series was further optimized by incorporating the 3-fluoro substituent (**17d**; fXa K_i = 0.48 nM). Most notable was the improvement in the Caco-2 permeability displayed by analogues **17c** and **17d**, which have P_{app} values of 1.20×10^{-6} cm/s and 3.14×10^{-6} cm/s, respectively (Table 6). The introduction of the trifluoromethyl pyrazole into the benzylamine P_1 series provides compounds with improved potency and an SAR which parallels that observed for the methylpyrazole benzylamine P_1 series. The most potent compound was **17h** (K_i = 0.15 nM) which contains the same P_4 substituent as **17d**. More importantly the Caco-2 permeability for

17h (P_{app} = 4.86×10^{-6} cm/sec) improves significantly. All compounds produced good selectivity ratios for fXa relative to thrombin and trypsin. Against relevant human enzymes, **17h** showed greater than 10000-fold selectivity for inhibition of fXa over thrombin and 300-fold selectivity over trypsin and kallikrein.[29] In the activated partial thromboplastin time (APTT) in vitro clotting assay, the methylpyrazole benzylamine P_1 analogues (Table 5) displayed clotting times within 2- to 3-fold when compared to benzamidine **2b** and are slightly higher for the trifluoromethyl analogues. The higher protein binding exhibited by the trifluoromethyl pyrazole analogues (Table 5) over their 3-methyl pyrazole counterparts may account at least in part for these changes. In the rabbit arterio-venous shunt thrombosis model, the benzylamine analogues exhibit good antithrombotic potency with ID_{50} values in the range of 0.6–
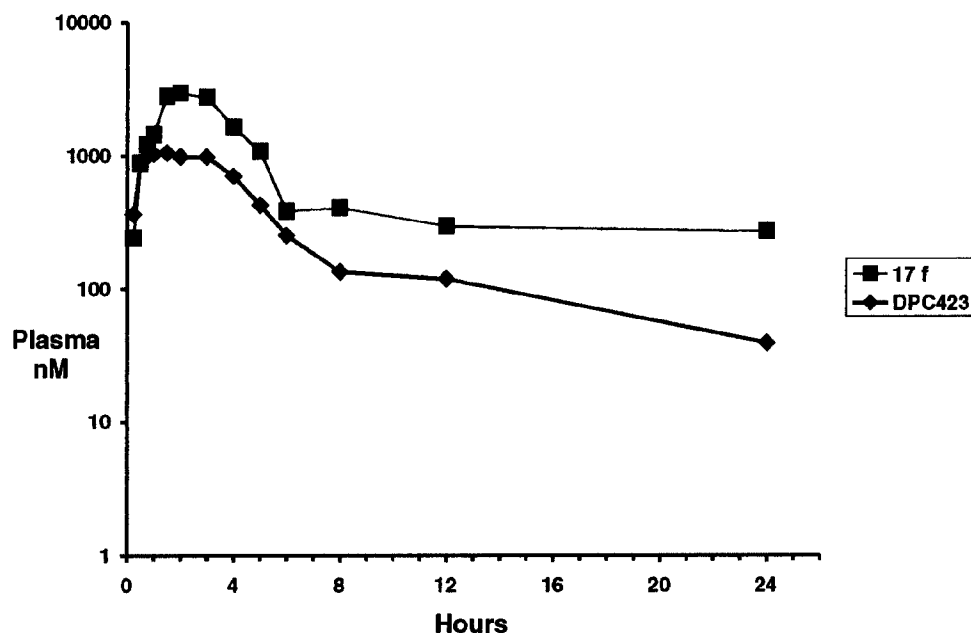
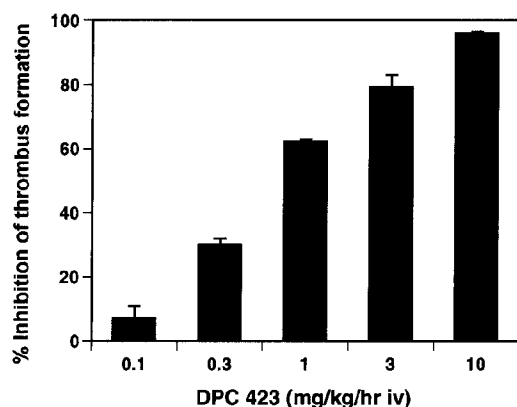**Figure 5.** In vivo dog pharmacokinetics of DPC423 (**17h**) and **17f**.

Figure 6. Antithrombotic effect of DPC423 (**17h**) in the rabbit arterio-venous shunt thrombosis model.

2.2 μmol/kg/h (Table 5). With the high binding affinity and good selectivity relative to thrombin and trypsin coupled with the good Caco-2 permeability and anti-thrombotic potency for these benzylamine analogues in hand, we next addressed the pharmacokinetic properties of the benzylamines.

Pharmacokinetic Profile of Benzylamine Analogues. When methyl pyrazole sulfonamide **17a** was dosed via intravenous administration to beagle dogs, low clearance and long half-life were observed (Table 6). However, when dosed orally the compound demonstrated relatively low oral availability, again consistent with the low measured Caco-2 permeability. The 3-fluoro analogue **17b** also displayed low clearance and poor oral absorption profile. Good oral bioavailability (73%) was seen for **17d**. Unfortunately, the high clearance and short duration of action made this compound unsuitable for further evaluation. Most of the 3-tri-fluoromethylpyrazole benzylamine analogues show good oral absorption and significantly longer duration of action. The best profile was observed with **17h**, which had a lower clearance (0.24 L/kg/h) and a slightly larger volume of distribution (V_{dss}) than the corresponding

Table 7. Selectivity Profile for DPC423 (**17h**)
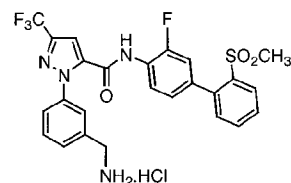
DPC 423

human enzymes	K_i (nM)
factor Xa	0.15 ± 0.02
trypsin	60 ± 6.5
thrombin	6000
plasma kallikrein	61[a]
activated protein C	1800[a]
factor IXa	2200 ± 0.2[a]
factor VIIa	> 15000[a]
chymotrypsin	> 17000[a]
urokinase	> 19000[a]
plasmin	> 35000[a]
tPA	> 45000[a]
complement factor I IC$_{50}$	44000[a]

[a] Data from **17h** TFA salt, others from HCl salt.

sulfonamide **17f**. These differences resulted in a longer exposure ($t_{1/2}$ of 7.5 h compared to 4.7 h) (Figure 5). When dosed orally, **17h** showed higher oral bioavailability (F% = 57%) compared to the corresponding sulfonamide **17f** (F% = 22%) and the des-fluoro analogue **17g** (F% = 39%; Table 6).

In rats, a higher total body clearance (5.1 ± 0.75 L/h/kg) and V_{dss} (21 ± 1.9 L/kg) was observed for 17 h. The terminal elimination half-life in rats was 4.6 ± 0.7 h (mean ± SD; n = 3). When dosed orally to rats, the plasma concentrations are lower and more variable than those encountered in dogs. The apparent oral bioavailability of **17h** in rats is 36%.

Compound **17h** was shown to be 89% protein bound as measured in human plasma by equilibrium dialysis. In the rabbit arterio-venous shunt thrombosis model, the compound inhibits thrombus formation with an ID$_{50}$

= 1.1 μmol/kg/h and with a IC_{50} (concentration to inhibit thrombus formation by 50%) value of 0.15 μM (Figure 6).[30] The IC_{50} value obtained for **17h** in the rabbit thrombosis models reflects its potency in this model.[31] Overall, compound **17h** showed the best balance of good permeability resulting in good oral bioavailability, low clearance, and relatively long half-life. When combined with its exceptionally good fXa potency and selectivity, **17h** emerged as an ideal candidate for further development as an antithrombotic agent (Table 7). DPC 423, a crystalline nonhygroscopic hydrochloride salt form of **17h**, was selected for clinical development.

Conclusions

Optimization of the core template of our fXa inhibitors led to a highly potent pyrazole analogue **2b**. Further optimization resulted in benzamidine analogues such as **14d** and **14f**, which are the most potent fXa inhibitors reported in the literature to date. While the benzamidine analogues demonstrated good factor Xa potency and selectivity, poor oral bioavailability and relatively short duration of action precluded further development of these compounds. Incorporation of a less basic benzylamine P_1 with a pK_a of ~8.8, followed by careful SAR manipulations resulted in the identification of analogue **17h**, a highly potent, selective, and orally bioavailable inhibitor of fXa. This compound is a potent antithrombotic agent which inhibits thrombus formation in a dose dependent manner. The nonhygroscopic hydrochloride salt form DPC 423 was selected for clinical development.

Experimental Section

Preparations of the final products and intermediates are included as Supporting Information. All reactions were run under an atmosphere of dry nitrogen. All solvents were used without purification as acquired from commercial sources. NMR spectra were obtained with a Varian VXR-300a spectrometer. Microanalyses were performed by Quantitative Technologies Inc. and were within 0.4% of the calculated values. Mass spectra were obtained on a HP 5988A MS/HP particle beam interface. Flash chromatography was done using EM Science silica gel 60. HPLC purifications were performed on a Ranin Dynamax SD200 instrument using a C18 reverse phase column with acetonitrile/water (containing 0.05% TFA) as a mobile phase. HPLC purity in most cases was >95%. Various P4 starting materials such as 4-amino[1,1-biphenyl]-2-*tert*-butylsulfonamide, 4-amino-3-fluoro[1,1-biphenyl]-2-*tert*-butylsulfonamide, 3-fluoro-2-(methylsulfonyl)[1,1-biphenyl]-4-amine, 2-(6-amino-3-pyridinyl)benzene-*tert*-butylsulfonamide, 2-(6-amino-3-pyrimidinyl)benzene-*tert*-butylsulfonamide substituted aminobiaryls, and aminopyridylphenylsulfonamides were obtained as per procedures described by Quan.[14a–c]

Ethyl-1-(3-cyanophenyl)-3-methyl-1*H*-pyrazole-5-carboxylate (4a) and 1-(3-Cyanophenyl)-3-methyl-1*H*-pyrazole-5-carboxylic Acid (4b). A solution of 3-cyanophenylhydrazine hydrochloride (3.38 g, 19.98 mmol) and methyl-4-(dimethylamino)-2-oxo-3-butenoate (3.14 g, 19.98 mmol) in acetic acid (75 mL) was refluxed for 18 h. The solution was concentrated and the residue chromatographed on silica gel (hexane/ethyl acetate, 8:2) to afford the desired pyrazole regioisomer **4a** (0.81 g, 17%). LRMS (ESI+): 242 (M + H). 1H NMR (CDCl3) δ: 3.77 (s, 3H), 4.20 (q, 2H), 7.16 (d, J = 1.5 Hz, 1H), 7.68 (t, 1H), 7.84 (m, 2H), 7.92 (dd, J = 2 and 8 Hz, 1H), 8.08 (d, J = 2.1 Hz, 1H). The above solid was saponified with LiOH (0.010 g, 0.2 mmol) in a THF/water solution (4:1, 25 mL). The reaction mixture was acidified with HCl (1 N), and the organics were extracted with ethyl acetate (2 × 50 mL), dried (magnesium sulfate), and evaporated to a colorless solid **4b** (0.70 g, 98%). LRMS (ESI+): 214 (M + H). 1H NMR

(CDCl3) δ: 7.16 (d, J = 1.5 Hz, 1H), 7.68 (t, 1H), 7.84 (m, 2H), 7.92 (dd, J = 2 and 8 Hz, 1H), 8.08 (d, J = 2.1 Hz, 1H).

1-{3-[Amino(imino)methyl]phenyl}-N-[2-(aminosulfonyl) [1,1-biphenyl]-4-yl]-3-methyl-1*H*-pyrazole-5-carboxamide, Trifluoroacetic Acid Salt (2a). The pyrazole **4b** (0.20 g, 0.92 mmol) was coupled according to the method described by Quan et al.[14b,c] to 4-amino[1,1-biphenyl]-2-*tert*-butylsulfonamide (0.28 g, 0.92 mmol) to afford **5** (0.36 g, 76%). LRMS (ESI+): 500 (M + H)+. 1H NMR (CDCl3) δ: 1.04 (s, 9H), 3.88 (s, 1H), 7.05 (s, 1H), 7.18–7.37 (m, 3H), 7.59–7.77 (m, 4H), 7.83 (dd, J = 2.5 and 8 Hz, 1H), 7.80 (m, 2H), 8.02 (m, 2H). Compound **5** was dissolved in dry methanol (10 mL) and cooled to 0 °C. Into this solution was bubbled dry HCl gas for 15 min. The reaction mixture was sealed and stirred at room temperature for 18 h. Removal of solvents in vacuo afforded the imidate intermediate which was immediately treated with a saturated solution of ammonia in methanol (10 mL). The reaction mixture was stirred at room temperature for 12 h, concentrated, and the crude benzamidine purified by reverse phase HPLC to afford 0.15 g of pyrazole benzamidine **2a** (45%) as the TFA salt. LRMS (ESI+): 461 (M + H). 1H NMR (DMSO-d6) δ: 7.23–7.38 (m, 5H), 7.56–7.78 (m, 5H), 7.80–7.86 (dt, J = 1.4 and 10 Hz, 2H), 7.93 (d, J = 1.9 Hz, 1H), 8.01 (dd, J = 1.9 and 12 Hz, 2H), 9.06 (bs, 2H), 9.45 (bs, 2H), 10.70 (s, 1H). HRMS (C23H20N6O3S): calcd 461.2678; found, 461.2587. HPLC purity >95%. Anal. calcd for C23H20N6O3S·1.3TFA·0.2H2O: C, 50.21, H, 3.57, N, 13.72; found, C, 50.11, H, 3.65, N, 13.88.

Ethyl-1-(3-cyanophenyl)-3-methyl-pyrazol-5-yl-carboxylate (6). Prepared in 75% yield following the methodology of Ashton.[18] LRMS (CI/NH3): 256 (M + H). 1H NMR (CDCl3) δ: 1.31 (t, 3H), 2.36 (s, 3H), 4.3 (q, 2H), 6.86 (s, 1H), 7.58 (t, 1H), 7.70 (dd, 1H), 7.76 (t, 1H).

1-(3-Cyanophenyl)-3-methyl-1*H*-pyrazol-5-ylcarboxylic Acid (6a). Ethyl-1-(3-cyanophenyl)-3-methyl-pyrazol-5-yl-carboxylate (0.55 g, 2.1 mmol) was dissolved in THF (20 mL) and to this was added LiOH (0.5 M, 5,6 mL). The reaction mixture was stirred at room temperature for 18 h, quenched with water (50 mL), and extracted with ethyl acetate (2 × 50 mL). The aqueous layer was acidified, and the organics were extracted with ethyl acetate (2 × 50 mL), dried (magnesium sulfate), and evaporated to afford pure acid (0.44 g, 90%). LRMS (CI/NH3): 228 (M + H). 1H NMR (DMSO-d6) δ: 2.27 (s, 3H), 6.89 (s, 1H), 7.09 (t, 1H), 7.82 (dd, 1H), 7.91 (d, 1H), 8.02 (t, 1H).

1-(3-Cyanophenyl)-N-[2-(*tert*-butylaminosulfonyl) [1,1-biphenyl]-4-yl]-3-methyl-1*H*-pyrazole-5-carboxamide, Trifluoroacetic Acid Salt (8). To a dichloromethane solution (20 mL) of 1-(3-cyanophenyl)-3-methyl-pyrazol-5-yl carboxylic acid (0.2 g, 0.88 mmol) was added oxalyl chloride (0.12 mL, 1.32 mmol). The reaction mixture was stirred at room temperature for 2 h. To this solution was then added 4-amino-[1,1-biphenyl]-2-*tert*-butylsulfonamide (0.27 g, 0.88 mmol) and triethylamine (0.50 mL), and the reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with water (50 mL), extracted with ethyl acetate (2 × 50 mL), washed with brine (50 mL), and dried (magnesium sulfate). Evaporation in vacuo afforded an oil which was chromatographed on silica gel (CH2Cl2:MeOH, 9:1) to afford the title compound (0.39 g, 99%). LRMS (ESI−): 458 (M − H). 1H NMR (CDCl3) δ: 1.03 (s, 9H), 2.42 (s, 3H), 3.64 (s, 1H), 6.76 (s, 1H), 7.30 (d, 1H), 7.50 (m, 3H), 7.58 (m, 2H), 7.68 (d, J = 7.8 Hz, 3H), 7.76 (d, J = 8.2 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 8.05 (s, 1H), 8.16 (d, J = 8.0 Hz, 1H).

1-{3-[Amino(imino)methyl]phenyl}-N-[2-(aminosulfonyl) [1,1-biphenyl]-4-yl]-3-methyl-1*H*-pyrazole-5-carboxamide (2b). Compound **8** (0.39 g, 0.85 mmol) was dissolved in anhydrous MeOH (20 mL) saturated with HCl. The reaction mixture was stirred at room temperature for 24 h and concentrated and the residue redissolved in MeOH (20 mL). Ammonium carbonate was added (1.0 g, 10.00 mmol), and the reaction mixture was stirred at room temperature for 18 h. Concentration followed by purification of the residue via reverse phase HPLC afforded pyrazole **2b** (0.15 g, 36%). LRMS (ESI+): 475 (M + H). 1H NMR (DMSO-d6) δ: 2.50 (s, 3H), 7.03

(s, 1H), 7.27 (s, 2H), 7.32 (d, $J = 8.5$ Hz, 1H), 7.37 (d, $J = 8.3$ Hz, 2H), 7.62 (m, 2H), 7.70 (d, $J = 7.8$ Hz, 2H), 7.75 (d, $J = 8.2$ Hz, 1H), 7.83 (t, 1H), 7.97 (s, 1H), 8.03 (d, 1H), 9.09 (s, 2H), 9.44 (s, 2H), 10.66 (s, 1H). HRMS ($C_{24}H_{23}N_6O_3S$): calcd 475.1552; found, 475.1537. HPLC purity >95%. Anal. calcd for $C_{24}H_{22}N_6O_3S \cdot 1.0$TFA: C, 53.06, H, 3.94, N, 14.28; found, C, 53.07, H, 3.89, N, 14.10.

1-(3-Cyanophenyl)pyrrole (15a). 2,5-Dimethoxytetrahydrofuran (0.44mol, 59.5 mL) was added to an acetic acid (200 mL) solution of 3-aminobenzonitrile (47.45 g, 0.40 mol). The solution was stirred at reflux overnight, allowed to cool to room temperature, and diluted with ethyl acetate (250 mL). The combined ethyl acetate layers were washed with brine (3 × 200 mL) and saturated sodium carbonate (200 mL), dried over magnesium sulfate, and filtered through a plug of silica gel. Evaporation in vacuo afforded the title compound (62.82 g, 93%). LRMS (H_2O-CI): 169 (M + H). ^{1}H NMR (CDCl$_3$) δ: 6.41 (t, $J = 2.2$ Hz, 2H), 7.09 (t, $J = 2.2$ Hz, 2H), 7.51–7.55 (m, 2H), 7.60–7.66 (m, 2H).

1-(3-Cyanophenyl)pyrrole-2-carboxaldehyde (15b). Phosphorus oxy-chloride (191.8 mmol, 17.90 mL) was added over 0.5 h to N,N-dimethylformamide (191.8 mmol, 14.1 mL) at 0 °C. The reaction mixture was cooled to 0 °C and diluted with 1,2-dichloroethane (100 mL). A solution of 1-(3-cyanophenyl)pyrrole (29.33g, 174.4 mmol) in 1,2-dichloroethane (250 mL) was added slowly via an addition funnel, and the mixture was heated to reflux for 0.5 h. The solution was cooled to room temperature, and to this mixture were added sodium acetate (86.55 g, 1.05 mol) and water (250 mL). The solution was heated to reflux for 0.5 h, diluted with ethyl acetate (250 mL), washed with brine (25 mL) and saturated aqueous sodium carbonate (250 mL), dried over magnesium sulfate, filtered through a plug of silica gel, and evaporated in vacuo to afford a brown solid. Recrystallization with ethyl acetate afforded the title compound as tan solid (28.4 g, 83%). LRMS (NH$_3$–CI): 214 (M + NH$_4$). ^{1}H NMR (CDCl$_3$) δ: 6.44–6.47 (m, 1H), 7.07 (d, $J = 1.1$ Hz, 1H), 7.17 (dd, $J = 3.7$ and 1.5 Hz, 1H), 7.54–7.71 (m, 4H), 9.58 9s, 1H).

1-(3-Cyanophenyl)-N-[2-(*tert*-butylaminosulfonyl)[1,1-biphenyl]-4-yl]-N-methyl-1H-pyrrole-2-carboxamide, (R = H, 16a). A solution of 1-(3-cyanophenyl)pyrrole-2-carboxaldehyde (5.14 g, 26.20 mmol) and acetone/water (1:1, 300 mL) was cooled to 0 °C. To this solution was added potassium permanganate (12.42 g, 78.60 mmol) over 0.5 h, and the reaction mixture was allowed to warm to room temperature. The mixture was quenched with sodium bisulfite (10.90 g, 104.8 mmol), and the solution was made acidic with HCl (10%). The solution was filtered through a plug of Celite, extracted with ethyl acetate (3 × 100 mL), washed with brine (200 mL), dried over magnesium sulfate, and evaporated in vacuo to afford the corresponding carboxylic acid derivative **15c** (4.11 g, 74%) as a colorless solid. LRMS (ESI$^-$): 211.2 (M – H). The 1-(3-cyanophenyl)pyrrole-2-carboxylic acid (2.77 g, 13.05 mmol) obtained above was dissolved in anhydrous DMF (50 mL), and to this mixture were added triethylamine (1.98 mL, 19.58 mmol), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluoro-phosphate (8.66 g, 19.58 mmol), and 4-amino[1,1-biphenyl]-2-*tert*-butylsulfonamide (6.03 g, 19.84 mmol). The reaction mixture was heated at 50 °C for 18 h, cooled to room temperature, and quenched with water (200 mL). The organics were extracted with ethyl acetate (2 × 100 mL), washed with brine (100 mL), dried over magnesium sulfate, and concentrated in vacuo. Purification of the residue via flash chromatography (hexane/ethyl acetate, 3:2) afforded the title compound (1.9 g, 29%). LRMS (NH$_3$–CI): 516 (M + NH$_4$). ^{1}H NMR (CDCl$_3$) δ: 1.01 (s, 9H), 3.67 (bs, 1H), 6.38 (dd, $J = 3.7$ and 2.9 Hz, 1H), 6.96–6.98 (m, 2H), 7.28 (dd, $J = 7.7$ and 1.5 Hz, 1H), 7.43–7.49 (m, 2H), 7.51–7.66 (m, 8H), 7.94 (bs, 1H), 8.15 (dd, $J = 7.8$, 1.3 Hz, 2H).

1-{3-[Amino(imino)methyl]phenyl}-N-[2-(aminosulfonyl)[1,1-biphenyl]-4-yl]-N-methyl-1H-pyrrole-2-carboxamide, Trifluoroacetic Acid Salt (3a). To a cold (0 °C) anhydrous methyl acetate (60mL) solution of **16a** (R = H, 0.37 g, 0.74 mmol) was added methanol (0.30 mL, 7.4 mmol).

Gaseous anhydrous HCl was bubbled through the solution for 0.5 h and allowed to stir overnight at room temperature. The reaction was concentrated in vacuo, and the residue was redissolved in anhydrous methanol (100 mL). Ammonium carbonate (0.43 g, 4.45 mmol) was added and the reaction mixture stirred overnight at room temperature. Evaporation in vacuo afforded a solid mass which was purified via reverse phase HPLC to afford the title compound as a colorless solid. LRMS: (ESI$^+$): 460.3 (M + H). ^{1}H NMR (DMSO-d_6) δ: 6.39 (t, 1H), 7.15–7.17 (m, 1H), 7.20 (s, 2H), 7.25–7.31 (m, 4H), 7.48–7.57 (m, 2H), 7.60–7.64 (m, 4H), 7.74–7.78 (m, 1H), 7.84 (bs, 1H), 7.98 (dd, $J = 7.7$, 1.4 Hz), 9.14 (bs, 2H), 9.38 (bs, 2H). HPLC purity >95%. HRMS ($C_{24}H_{22}N_5O_3S$): calcd 460.1443; found, 460.1447.

1-(3-Cyanophenyl)-2-formyl-4-bromopyrrole. 1-(3-Cyanophenyl) pyrrole-2-carboxaldehyde (6.06 g, 30.89 mmol) was combined with N-bromosuccinimide (6.60 g, 37.06 mmol) in anhydrous CCl$_4$ (150 mL) and stirred at room temperature overnight. The residue was treated with ethyl acetate (50 mL), filtered through a silica gel, and concentrated in vacuo. The residue was then recrystallized from ethyl acetate to afford the title compound as a light brown solid (4.49 g, 53%). LRMS (CI/NH$_3$): 292 (M + NH$_4$). ^{1}H NMR (CDCl$_3$) δ: 7.06 (dd, $J = 1.8$, 0.9 Hz, 1H), 7.14 (d, $J = 2.0$ Hz, 1H), 7.57–7.60 (m, 2H), 7.62–7.63 (m, 1H), 7.72–7.75 (m, 1H), 9.52 (d, $J = 0.8$ Hz, 1H). HPLC purity >95%.

1-{3-[Amino(imino)methyl]phenyl}-N-[2-(aminosulfonyl)[1,1-biphenyl]-4-yl]-4-bromo-N-methyl-1H-pyrrole-2-carboxamide, Trifluoroacetic Acid Salt (3b). Following the procedures described above, 1-(3-cyanophenyl)-2-formyl-4-bromopyrrole was converted into the title compound. LRMS (ESI$^+$): 538.2 (M + H). ^{1}H NMR (DMSO-d_6) δ: 7.21 (s, 2H), 7.24–7.30 (m, 4H), 7.51 (s, 2H), 7.54–7.57 (m, 1H), 7.62–7.66 (m, 4H), 7.77–7.80 (m, 1H), 7.86 (bs, 1H), 7.98 (d, $J = 7.3$ Hz, 1H), 9.01 (bs, 2H), 9.36 (bs, 2H); HPLC purity >95%. HRMS ($C_{24}H_{21}BrN_5O_3S$): calcd 538.054; found, 538.055.

Preparation of 1-(3-Cyanophenyl)-3-trifluoromethylpyrazole-5-carboxylic Acid (12). A solution of 1,1,1-trifluoro-2,4-pentanedione (1.35 mL, 11.2 mmol), 3-bromophenylhydrazine hydrochloride (3 g, 13.4 mmol) in glacial acetic acid (20 mL), and 2-methoxyethanol (10 mL) was heated to reflux for 2 h. The solvents were removed in vacuo, and the residue was dissolved in ethyl acetate (100 mL). The ethyl acetate solution was washed with 1 N HCl (10 mL), saturated NaHCO$_3$ (50 mL), and brine (50 mL) and dried (magnesium sulfate). Purification via silica gel flash chromatography [hexanes/ethyl acetate (8:1)] afforded the pyrazole intermediates **9a** and **9b** as a 8:2 mixture of the two isomers (3.42 g, 100%), the desired 5-methylpyrazole isomer pre-dominating. The mixture was combined with 1-methyl pyrrolidinone (7 mL) and copper cyanide (1.3 g, 14.5 mmol) and heated to reflux for 18 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL), and filtered. The filtrate was washed with water (100 mL) and brine (50 mL) and dried (magnesium sulfate). The crude mixture was purification via silica gel flash chromatography (hexane ethyl acetate, 9:1) to afford a mixture of cyanophenyl intermediates **10a** and **10b** (1.15 g, 40%). To the mixture of **10a** and **10b** (0.65 g, 2.59 mmol) in carbon tetrachloride (20 mL) was added N-bromosuccinimide (0.48 g, 2.7 mmol) and benzoylperoxide (20 mg). The reaction mixture was refluxed for 6 h, cooled, filtered, and concentrated to yield the crude bromide. The bromide was dissolved in a mixture of dioxane/water (1:1, 20 mL), and calcium carbonate (0.46 g, 4.6 mmol) was added. The solution was heated on a steam bath for 6 h, cooled, filtered, and concentrated in vacuo. Purification via silica gel flash chromatography (hexanes/ethyl acetate, 1:1) afforded the desired alchohol **11a** (0.31 g, 44%). LRMS (CI–NH$_3$): 268.1 (M + H), 285 (M + NH$_4$). ^{1}H NMR (CDCl$_3$) δ: 8.07 (s, 1H), 8.01 (dd, $J = 2.2, 8.05$ Hz, 1H), 7.77 (d, $J = 7.7$ Hz, 1H), 7.68 (t, $J = 8.05$ Hz, 1H), 6.76 (s, 1H), 4.72 (d, $J = 5.85$ Hz, 2H), 2.02 (t, $J = 5.86$ Hz, 1H). To **11a** (0.18 g, 0.67 mmol) in acetonitrile (5 mL) was added sodium periodate (0.3 g, 1.4 mmol), water (5 mL), and a crystal of ruthenium(III)chloride hydrate. The reaction

was stirred for 18 h at room temperature, filtered, and concentrated in vacuo. The aqueous solution was extracted with ethyl acetate (2 × 50 mL) and evaporated to afford the desired carboxylic acid **13** (0.17 g, (89.9%)). LRMS (ESI⁻): 280.2 (M − H). ¹H NMR (CDCl₃ + DMSO-d_6) δ: 7.82 (d, J = 1.47 Hz), 7.78 (dd, J = 8.0, 1.47 Hz, 1H), 7.63 (t, J = 7.3, 8.42, 1H), 7.29 (s, 1H).

1-{3-[Amino(imino)methyl]phenyl}-N-[2-(aminosulfonyl)[1,1-biphenyl]-4-yl]-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide, Trifluoroacetic Acid Salt (14a). To the pyrazole carboxylic acid **12** (0.35 g, 1.2 mmol) dissolved in methylene chloride (50 mL) was added oxalyl chloride (0.15 mL, 1.7 mmol) and 2 drops of DMF. The reaction was stirred for 2 h at room temperature and concentrated in vacuo. The residue was redissolved in methylene chloride (10 mL). 4-Amino[1,1-biphenyl]-2-*tert*-butylsulfonamide (0.38 g, 1.25 mmol) and *N*,*N*-dimethylaminopyridine (0.38 g, 3.1 mmol) were added, and the reaction was stirred at room temperature for 24 h. The reaction was concentrated and the residue quenched with HCl (3 N, 50 mL). The organics were extracted with ethyl acetate (2 × 100 mL), washed with saturated NaHCO₃ (50 mL) and brine (50 mL), and dried (magnesium sulfate). The crude product was purified via silica gel flash chromatography (hexanes/ethyl acetate, 1:1) to afford the desired coupled product 0.41 g (58%). LRMS (ESI⁺): 590 (M + Na). ¹H NMR (CDCl₃ + DMSO-d_6) δ: 9.88 (s, 1H), 8.18 (dd, J = 7.69, 1.47 Hz, 1H), 7.87 (d, J = 1.83 Hz, 1H), 7.79 (m,4H), 7.64 (m, 3H), 7.50 (m, 3H), 7.30 (d, J = 7.3 Hz, 1H), 3.67 (s, 1H), 1.02 (s, 9H). Following the Pinner amidine reaction described previously, the desired product **14a** was obtained (46%). LRMS (ESI⁺): 529.03 (M + H). ¹H NMR (DMSO-d_6) δ: 10.85 (s, 1H), 9.47 (s, 1.5H), 9.20 (s, 1.5H), 8.05 (s, 1H), 8.04 (dd, J = 7.69, 1.84 Hz, 1H), 7.96 (m, 2H), 7.82 (d, J = 7.69 Hz, 1H), 7.75 (s, 1H), 7.68 (d, J = 8.79 Hz, 2H), 7.62 (m, 2H), 7.39 (d, J = 8.43 Hz, 2H), 7.32 (sm, 3H). HRMS (C₂₄H₂₀F₃N₆O₃S): calcd 529.1270, found, 529.1267. HPLC purity >95%. Anal. calcd for C₂₄H₁₉F₃N₆O₃S·1.2TFA·1.0H₂O; C, 46.40; H, 3.27; N, 12.30; found, C, 46.11; H,3.06; N, 12.05.

1-[3-(Aminomethyl)phenyl]-N-[2-(aminosulfonyl)[1,1-biphenyl]-4-yl]-3-methyl-1H-pyrazole-5-carboxamide, trifluoroacetic Acid Salt (17a). 1-(3-Cyanophenyl)-5-[(2-aminosulfonyl-[1,1]-biphen-4-yl)aminocarbonyl]-3-methylpyrazole **13a** (0.19 g, 0.41 mmol) was dissolved in ethanol (20 mL). To this solution was added TFA (0.5 mL) and palladium on carbon (10%, 10 mg), and the mixture was hydrogenated on a Parr apparatus at 40 psi for 18 h. The mixture was filtered, concentrated, and purified by reverse phase HPLC to afford the title compound **17a** (17 mg, 9%). LRMS (ESI⁺): 462 (M + H). ¹H NMR (DMSO-d_6) δ: 10.66 (s, 1H), 8.22 (bd, 2H), 8.03 (dd, J = 1.47, 6.22 Hz, 1H), 7.70 (d, J = 8.79 Hz, 2H), 7.67 (m, 2H), 7.64 (m, 5H), 7.37 (d, J = 8.43 Hz, 2H), 7.32 (m, 2H), 6.93 (s, 1H), 4.13 (d, J = 4.03 Hz, 2H), 2.33 (s, 3H). HRMS (C₂₄H₂₄N₅O₃S): calcd 462.1599; found, 462.1589. HPLC purity >95%. Anal. calcd for C₂₄H₂₃N₅O₃S·1.0TFA·1.5H₂O; C, 51.82, H, 4.52, N, 11.62; found, C, 51.80, H, 4.35, N, 11.29.

1-[3-(Aminomethyl)phenyl]-N-[3-fluoro-2-(methylsulfonyl)[1,1-biphenyl]-4-yl]-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide, Trifluoroacetic Acid Salt (17h). Prepared following the procedure for **17a**. LRMS (ESI⁺) 532 (M + H). ¹H NMR (DMSO-d_6) δ: 10.75 (s, 1H), 8.23 (m, 3H), 8.11 (dd, J = 7.69 and 1.46 Hz, 1H), 7.96 (dd, J = 6.96, 1.47 Hz, 1H), 7.81 (m, 8H), 7.26 (dd, J = 1.47 and 8.06 Hz, 1H), 4.16 (q, J = 5.49 Hz, 2H), 2.94 (s, 3H). HRMS (C₂₅H₂₁F₄N₄O₃S): calcd 533.1192; found, 533.1279. HPLC purity >95%. Anal. calcd for C₂₅H₂₀F₄N₄O₃S·1.1TFA; C, 49.65, H, 3.23, N, 8.52, found, C, 49.73, H, 2.98, N, 8.40.

1-[3-(Aminomethyl)phenyl]-N-[3-fluoro-2-(methylsulfonyl)[1,1-biphenyl]-4-yl]-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide, Hydrochloride Salt (DPC423). Compound **17h** (0.47 g, 0.727 mmol) was dissolved in absolute methanol (30 mL). The mixture was cooled to 0 °C, and dry HCl gas was bubbled for 15 min. To this solution was added diethyl ether (400 mL) upon which a white solid precipitated. The solid

was collected and recrystallized from MeOH/EtOAc to afford 0.34 g (82.9%) of a colorless crystalline solid. mp: 288 °C. ¹H NMR (DMSO-d_6) δ: 10.83 (s, 1H), 8.44 (s, 2H), 8.11 (dd, J = 1.1, 7.7 Hz, 1H), 7.81 (m, 6H), 7.62 (m, 2H), 7.44 (dd, J = 1.1, 7.3 Hz, 1H), 7.41 (dd, J = 1.8, 11.4, 1H), 7.25 (dd, J = 1.5, 8.1 Hz, 1H), 4.13 (s, 2H), 2.94 (s, 3H). HRMS (C₂₅H₂₁F₄N₄O₃S): calcd 533.1192; found, 533.1282; HPLC purity > 95%; Anal. calcd for C₂₅H₂₁F₄N₄O₃S₁·1.0HCl; C, 52.77, H, 3.72, N, 9.85, Cl, 6.23; found, C, 52.86, H, 3.45, N, 9.74, Cl, 6.30.

Supporting Information Available: Experimental data for compounds **2c−2n**, **14b−14f**, **17b−17f**, and all relevant biological protocols. This material is available free of charge via the Internet at http://pubs.acs.org.

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LEXSEE

THE PROCTER & GAMBLE COMPANY, Plaintiff-Appellee, v. TEVA PHARMACEUTICALS USA, INC., Defendant-Appellant.

2008-1404, 2008-1405, 2008-1406

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

2009 U.S. App. LEXIS 10475

May 13, 2009, Decided

PRIOR HISTORY: [*1]

Appeal from the United States District Court for the District of Delaware in 04-940, 08-066, and 08-191, Judge Joseph J. Farnan, Jr.
P&G v. Teva Pharms. USA, Inc., 536 F. Supp. 2d 476, 2008 U.S. Dist. LEXIS 15127 (D. Del., 2008)

DISPOSITION: AFFIRMED.

CASE SUMMARY:

PROCEDURAL POSTURE: Defendant appealed from a decision of the United States District Court for the District of Delaware that found in favor of plaintiff patentee in three cases upholding the validity of *U.S. Patent 5,583,122 ('122 patent)*. The *'122 patent* claimed the compound risedronate, the active ingredient of the patentee's osteoporosis drug.

OVERVIEW: The district court properly found that a person of ordinary skill in the art would have identified 2-pyr EHDP as a lead compound for the treatment of osteoporosis based on the patentee's expired *U.S. Patent 4,761,406 ('406 patent)*. Even if 2-pyr EHDP was a lead compound, the evidence did not establish that it would have been obvious to a person of ordinary skill to modify 2-pyr EHDP to create risedronate. Every bisphosphonate compound, while remaining a bisphosphonate, exhibited its own physical-chemical, biological and therapeutic characteristics, so that each bisphosphonate had to be considered on its own. Thus, there was no reasonable

expectation in 1985, the year the *'406 patent* was granted, that risedronate would have been a successful compound based on prior compounds. There was no credible evidence that the structural modification that resulted in risedronate was routine. Looking to secondary considerations, risedronate satisfied a long-felt unmet need for osteoporosis as the existing treatments in 1985 were inadequate. Because risedronate was not obvious under *35 U.S.C.S. § 103*, the *'122 patent* was not invalid for obviousness-type double patenting.

OUTCOME: The appellate court affirmed the decision of the district court.

LexisNexis(R) Headnotes

Civil Procedure > Appeals > Standards of Review > Clearly Erroneous Review
Civil Procedure > Appeals > Standards of Review > De Novo Review
[HN1] On appeal from a bench trial, an appellate court reviews the district court's conclusions of law de novo and findings of fact for clear error.

Patent Law > Jurisdiction & Review > Standards of Review > Clearly Erroneous Review
Patent Law > Jurisdiction & Review > Standards of Review > De Novo Review
[HN2] Whether the subject matter of a patent is obvious

is a question of law and is reviewed de novo. Factual determinations underlying the obviousness issue are reviewed for clear error. The evidentiary burden to show facts supporting a conclusion of invalidity is one of clear and convincing evidence. Non-statutory double patenting is a legal question reviewed without deference.

Evidence > Procedural Considerations > Burdens of Proof > Clear & Convincing Proof
Patent Law > Nonobviousness > Elements & Tests > Ordinary Skill Standard
Patent Law > Nonobviousness > Elements & Tests > Prior Art
[HN3] Under the U.S. Patent Act, an invention cannot be patented if the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *35 U.S.C.S. § 103(a)*. Patents are presumed to be valid. A party seeking to invalidate a patent based on obviousness must demonstrate by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so. Clear and convincing evidence places in the fact finder an abiding conviction that the truth of the factual contentions are highly probable.

Patent Law > Nonobviousness > Elements & Tests > Ordinary Skill Standard
Patent Law > Nonobviousness > Elements & Tests > Prior Art
Patent Law > Nonobviousness > Elements & Tests > Secondary Considerations
[HN4] The obviousness determination turns on underlying factual inquiries involving: (1) the scope and content of prior art; (2) differences between claims and prior art; (3) the level of ordinary skill in pertinent art; and (4) secondary considerations such as commercial success and satisfaction of a long-felt need. The United States Supreme Court has explained that the United States Court of Appeals for the Federal Circuit's "teaching, suggestion or motivation" test provides helpful insight into the obviousness question as long as it is not applied rigidly. Accordingly, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.

Patent Law > Nonobviousness > Elements & Tests > Ordinary Skill Standard
Patent Law > Nonobviousness > Elements & Tests > Predictability
[HN5] If a patent challenger makes a prima facie showing of obviousness, the owner may rebut based on "unexpected results" by demonstrating that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.

Patent Law > Nonobviousness > Elements & Tests > Ordinary Skill Standard
Patent Law > Nonobviousness > Elements & Tests > Prior Art
[HN6] An obviousness argument based on structural similarity between claimed and prior art compounds clearly depends on a preliminary finding that one of ordinary skill in the art would have selected the prior art compound as a lead compound.

Patent Law > Nonobviousness > Elements & Tests > Prior Art
[HN7] The question of obviousness often turns on the structural similarities and differences between the claimed compound and the prior art compound. Precedent establishes the analytical procedure whereby a close structural similarity between a new chemical compound and prior art compounds is generally deemed to create a prima facie case of obviousness. Structural relationships often provide the requisite motivation to modify known compounds to obtain new compounds.

Patent Law > Nonobviousness > Elements & Tests > Predictability
Patent Law > Nonobviousness > Elements & Tests > Prior Art
[HN8] To successfully argue that a new compound is obvious, the challenger may show that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention. In keeping with the flexible nature of the obviousness inquiry, the requisite motivation to modify can come from any number of sources. Thus, in addition to structural similarity between the compounds, a prima facie case of obviousness may be shown by adequate support in the prior art for the change in structure. A known compound may suggest its homolog, analog, or

isomer because such compounds often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties. However, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.

Patent Law > Nonobviousness > Elements & Tests > Predictability
[HN9] To the extent an art is unpredictable, as the chemical arts often are, the focus on identified, predictable solutions may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.

Patent Law > Nonobviousness > Elements & Tests > Ordinary Skill Standard
Patent Law > Nonobviousness > Elements & Tests > Predictability
[HN10] The United States Supreme Court has stated that when an obvious modification leads to the anticipated success, the invention is likely the product of ordinary skill and is obvious under *35 U.S.C.S. § 103*. Obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.

Patent Law > Nonobviousness > Elements & Tests > Ordinary Skill Standard
Patent Law > Nonobviousness > Elements & Tests > Prior Art
[HN11] When a person of ordinary skill is faced with a finite number of identified, predictable solutions to a problem and pursues the known options within his or her technical grasp, the resulting discovery is likely the product not of innovation but of ordinary skill and common sense. So too, granting patent protection to advances that would occur in the ordinary course without real innovation retards progress. In other cases, though, researchers can only vary all parameters or try each of numerous possible choices until one possibly arrives at a successful result, where the prior art gives either no indication of which parameters are critical or no direction as to which of many possible choices is likely to be successful. In such cases, courts should not succumb to hindsight claims of obviousness. Similarly, patents are

not barred just because it was obvious to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Patent Law > Nonobviousness > Elements & Tests > Secondary Considerations
[HN12] Secondary considerations of non-obviousness include the commercial success of the invention at issue and its satisfaction of a long-felt need. The district court found that secondary considerations supported a finding of non-obviousness. When present, such factors may often be the most probative and cogent evidence of non-obviousness in the record.

Patent Law > Nonobviousness > Elements & Tests > Ordinary Skill Standard
[HN13] It is well established that when a party seeks to prove conception via the oral testimony of a putative inventor, the party must proffer evidence corroborating that testimony. The inventor must provide independent corroborating evidence in addition to his own statements and documents.

Patent Law > Double Patenting > Elements
[HN14] The double patenting doctrine is designed to prevent a patent owner from extending his exclusive rights to an invention through claims in a later-filed patent that are not patentably distinct from claims in the earlier filed patent. In general, the obviousness analysis applies to double patenting, except for three distinctions. First, statutory obviousness compares claimed subject matter to the prior art, while non-statutory double patenting compares claims in an earlier patent to claims in a later patent or application. Second, double patenting does not require inquiry into a motivation to modify the prior art. Finally, double patenting does not require inquiry into objective criteria suggesting non-obviousness.

COUNSEL: William F. Lee, Wilmer Cutler Pickering Hale & Dorr LLP, of Boston, Massachusetts, argued for plaintiff-appellee. With him on the brief were Vinita Ferrera and Allen C. Nunnally. Also on the brief were David B. Bassett and Christopher J. Meade, of New York, New York.

James Galbraith, Kenyon & Kenyon LLP, of New York, New York, argued for defendant-appellant. With him on the brief were Maria Luisa Palmese, and A. Antony Pfeffer.

JUDGES: Before MAYER, DYK, Circuit Judges, and HUFF, * District Judge.

> * Honorable Marilyn L. Huff, District Judge, United States District Court for the Southern District of California, sitting by designation.

OPINION BY: HUFF

OPINION

> HUFF, *District Judge*.

Teva Pharmaceuticals USA, Inc. ("Teva") appeals from a final judgment of the United States District Court for the District of Delaware in favor of The Procter & Gamble Company ("P&G") in three cases upholding the validity of P&G's *U.S. Patent 5,583,122* (the "*'122 patent*"). *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc., 536 F. Supp. 2d 476 (D. Del. 2008)*. After a bench trial and a stipulation for [*2] judgment in the related cases, the district court rejected Teva's invalidity defenses of obviousness and obviousness-type double patenting. We affirm.

I. BACKGROUND

The *'122 patent* claims the compound risedronate, the active ingredient of P&G's osteoporosis drug Actonel(R). In August 2004, P&G sued Teva for infringement of the *'122 patent* after Teva notified P&G that it planned to market risedronate as a generic equivalent of Actonel(R). Specifically, P&G alleged that Teva's proposed drug infringed claim 4 of the *'122 patent* for the compound risedronate, claim 16 for pharmaceutical compositions containing risedronate, and claim 23 for methods of treating diseases using risedronate. In its defense, Teva argued that the *'122 patent* was invalid as obvious in light of P&G's expired *U.S. Patent 4,761,406* (the "*'406 patent*"), filed on June 6, 1985 and issued on August 2, 1988. Alternately, Teva argues that the *'122 patent* is invalid for obviousness-type double patenting.

Risedronate, the subject of the contested claims, is a member of a group of compounds referred to as bisphosphonates. Bisphosphonates, in general, are active in inhibiting bone resorption. The first two promising bisphosphonates [*3] studied for the treatment of metabolic bone diseases, etidronate (EHDP) and clodronate, had clinical problems which prevented their commercialization. P&G conducted a significant amount of experimentation involving hundreds of different bisphosphonate compounds, but could not predict the efficacy or toxicity of the new compounds. Eventually, researchers at P&G identified risedronate as a promising drug candidate.

On December 6, 1985, risedronate's inventors applied for a patent on the compound. P&G is the owner by assignment of the *'122 patent*, entitled "Pharmaceutical Compositions Containing Geminal Diphosphonates," which issued on

Risedronate is neither claimed nor disclosed in the *'406 patent*. Instead, the *'406 patent*, entitled "Regimen for Treating Osteoporosis," claims an intermittent dosing method for treating osteoporosis. As the trial court noted, the *'406 patent* "addresses the central problem seen in bisphosphonates at the time, namely that they inhibited bone mineralization, by teaching the use of a cyclic administrative regimen to achieve a separation of the benign effect of anti-resorption from the unwanted side effect of anti-mineralization in patients." *Procter & Gamble, 536 F. Supp. 2d at 492*. [*4] The *'406 patent* lists thirty-six polyphosphonate molecules as treatment candidates and eight preferred compounds for intermittent dosing, including 2-pyr EHDP. Teva contends that the structural similarities between risedronate and 2-pyr EHDP render the challenged claims of the *'122 patent* obvious.

From the testimony at trial, the district court concluded that the *'406 patent* would not have led a person of ordinary skill in the art to identify 2-pyr EHDP as the lead compound. In light of the extremely unpredictable nature of bisphosphonates at the time of the invention, the district court also found that a person of ordinary skill in the art would not have been motivated to make the specific molecular modifications to make risedronate. The district court concluded that unexpected results of risedronate's potency and toxicity rebut a claim of obviousness. The district court found that secondary considerations of non-obviousness supported its conclusions. Similarly, the court found that the *'122 patent* was not invalid for obviousness-type double

patenting. This consolidated appeal followed. We have jurisdiction pursuant to *28 U.S.C. § 1295(a)(1)*.

II. DISCUSSION

I. Standard of Review

[HN1] "On appeal [*5] from a bench trial, this court reviews the district court's conclusions of law de novo and findings of fact for clear error." *Golden Blount, Inc. v. Robert H. Peterson Co., 365 F.3d 1054, 1058 (Fed. Cir. 2004)*. [HN2] Whether the subject matter of a patent is obvious is a question of law and is reviewed de novo. *PharmaStem Therapeutics, Inc. v. ViaCell, Inc., 491 F.3d 1342, 1359 (Fed. Cir. 2007)*. Factual determinations underlying the obviousness issue are reviewed for clear error. *Alza Corp. v. Mylan Labs., Inc., 464 F.3d 1286, 1289 (Fed. Cir. 2006)*. The evidentiary burden to show facts supporting a conclusion of invalidity is one of clear and convincing evidence. *AK Steel Corp. v. Sollac & Ugine, 344 F.3d 1234, 1238-39 (Fed. Cir. 2003)*. Non-statutory double patenting is a legal question reviewed without deference. *Georgia-Pacific Corp. v. U.S. Gypsum Co., 195 F.3d 1322, 1326 (Fed. Cir. 1999)*.

II. Patent Obviousness - Legal Standard

[HN3] Under the U.S. Patent Act, an invention cannot be patented if "the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." *35 U.S.C. § 103(a)*. Patents [*6] are presumed to be valid. *Kao Corp. v. Unilever U.S., Inc., 441 F.3d 963, 968 (Fed. Cir. 2006)*. A party seeking to invalidate a patent based on obviousness must demonstrate "by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1361 (Fed. Cir. 2007)*. Clear and convincing evidence places in the fact finder "an abiding conviction that the truth of [the] factual contentions are highly probable." *Colorado v. New Mexico, 467 U.S. 310, 316, 104 S. Ct. 2433, 81 L. Ed. 2d 247 (1984)* (quotation marks omitted).

[HN4] The obviousness determination turns on underlying factual inquiries involving: (1) the scope and content of prior art, (2) differences between claims and prior art, (3) the level of ordinary skill in pertinent art,

and (4) secondary considerations such as commercial success and satisfaction of a long-felt need. *Graham v. John Deere Co., 383 U.S. 1, 17, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966)*. The Supreme Court has explained that the Federal Circuit's "teaching, suggestion or motivation" test provides helpful [*7] insight into the obviousness question as long as it is not applied rigidly. *KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 127 S. Ct. 1727, 1741, 167 L. Ed. 2d 705 (2007)*. Accordingly, under *KSR*, "it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007)*.

[HN5] If a patent challenger makes a prima facie showing of obviousness, the owner may rebut based on "unexpected results" by demonstrating "that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995)*. We consider the relevant factors in turn.

III. Identification of a Lead Compound

[HN6] An obviousness argument based on structural similarity between claimed and prior art compounds "clearly depends on a preliminary finding that one of ordinary skill in the art would have selected [the prior art compound] as a lead compound." *Takeda, 492 F.3d at 1359*; *see also Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353, 1359 (Fed. Cir. 2008)* [*8] (stating that "post-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound" in the prior art). Teva argues that the *'406 patent* identifies 2-pyr EHDP as the most promising molecule for the inhibition of bone resorption. The trial court disagreed and concluded from the evidence that a person of ordinary skill in the art would not have identified 2-pyr EHDP as a lead compound for the treatment of osteoporosis.

We need not reach this question because we conclude that even if 2-pyr EHDP was a lead compound, the evidence does not establish that it would have been obvious to a person of ordinary skill at the time of the invention to modify 2-pyr EHDP to create risedronate.

IV. Obviousness of Risedronate in Light of the Prior

Art

To decide whether risedronate was obvious in light of the prior art, a court must determine whether, at the time of invention, a person having ordinary skill in the art would have had "reason to attempt to make the composition" known as risedronate and "a reasonable expectation of success in doing so." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc., 491 F.3d 1342, 1360 (Fed. Cir. 2007).*

The [*9] district court concluded that, even if 2-pyr EHDP were a lead compound, it would not render the *'122 patent*'s claims on risedronate obvious because a person having ordinary skill in the art would not have had reason to make risedronate based on the prior art. The district court's findings also support the conclusion that there could have been no reasonable expectation as to risedronate's success.

[HN7] The question of obviousness "often turns on the structural similarities and differences between the claimed compound and the prior art compound[]." *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353, 1356-57 (Fed. Cir. 2008)*; *see also Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075, 1086 (Fed. Cir. 2008)* ("Precedent establishes the analytical procedure whereby a close structural similarity between a new chemical compound and prior art compounds is generally deemed to create a prima facie case of obviousness . . . ."); *In re Mayne, 104 F.3d 1339, 1343 (Fed. Cir. 1997)* ("Structural relationships often provide the requisite motivation to modify known compounds to obtain new compounds."); *In re Payne, 606 F.2d 303, 313-15 (CCPA 1979)* (discussing the presumption of obviousness based on close [*10] structural similarity). In this case, risedronate and 2-pyr EHDP are positional isomers; they each contain the same atoms arranged in different ways. In risedronate, the hydroxy-ethane-diphosphonate group is connected to the # 3 carbon of a pyridine ring, while in 2-pyr EHDP, the hydroxy-ethane-diphosphonate group is connected to the # 2 carbon. Because the nitrogen atom is in a different position in the two molecules, they differ in three dimensional shape, charge distribution and hydrogen bonding properties.

[HN8] To successfully argue that a new compound is obvious, the challenger may show "that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." *Takeda, 492 F.3d at 1356* (quotation marks omitted). "In keeping with the flexible nature of the obviousness inquiry, the requisite motivation [to modify] can come from any number of sources." *Eisai, 533 F.3d at 1357* (citation omitted). Thus, in addition to structural similarity between the compounds, a prima facie case of obviousness may be shown by "adequate support in the prior art" for the change in structure. *In re Grabiak, 769 F.2d 729, 731-32 (Fed. Cir. 1985).* As we [*11] noted in *Takeda*:

> A known compound may suggest its homolog, analog, or isomer because such compounds often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties. . . . [However,] it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.

492 F.3d at 1356-57 (citation omitted).

At trial, P&G's expert witnesses testified that, in 1985, a person having ordinary skill in the art realized that the properties of bisphosphonates could not be anticipated based on their structure. Additionally, the trial court relied on contemporaneous writings from Herbert Fleisch, the preeminent authority on bisphosphonates during the relevant time period. Dr. Fleisch wrote in 1984 that "every compound, while remaining a bisphosphonate, exhibits its own physical-chemical, biological and therapeutic characteristics, so that each bisphosphonate has to be considered on its own. To infer from one compound the effects in another is dangerous and can be misleading." Herbert Fleisch, *Chemistry* [*12] *and Mechanisms of Action of Bisphosphonates, in* Bone Resorption, Metastasis, and Diphosphonates 33-40 (S. Garattini ed., 1985). In this case, P&G synthesized and tested 2-pyr EHDP, risedronate (3-pyr EHDP) and 4-pyr EHDP, another structural isomer. Confirming the unpredictability of bisphosphonates, test results for 4-pyr EHDP revealed that it was not active in inhibiting bone resorption despite its close relationship with potent compounds. In light of the Supreme Court's instruction in *KSR*, the Federal Circuit has stated that, [HN9] "[t]o the extent an art is unpredictable, as the chemical arts often are, *KSR's* focus on [] 'identified, predictable solutions'

may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai, 533 F.3d 1353, 1359* (quoting **KSR, 127 S. Ct. at 1742**). The district court found that Teva failed to clear that hurdle, establishing insufficient motivation for a person of ordinary skill to synthesize and test risedronate. This finding was not clearly erroneous.

Additionally, there was an insufficient showing that a person of ordinary skill in the art would have had a "reasonable expectation of success" in synthesizing and [*13] testing risedronate. *PharmaStem, 491 F.3d at 1360*. In *KSR*, [HN10] the Supreme Court stated that when an obvious modification "leads to the anticipated success," the invention is likely the product of ordinary skill and is obvious under *35 U.S.C. § 103*. **127 S. Ct. at 1742**. "[O]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, 480 F.3d at 1364* (citing *In re Corkill, 771 F.2d 1496, 1500 (Fed. Cir. 1985))*. Here, the district court's findings indicate that there was no reasonable expectation in 1985 that risedronate would be a successful compound.

Cases following *KSR* have considered whether a given molecular modification would have been carried out as part of routine testing. *See, e.g., Takeda, 492 F.3d at 1360* (discussing the district court's finding that a modification was not known to be beneficial and was not considered "routine"). [HN11] When a person of ordinary skill is faced with "a finite number of identified, predictable solutions" to a problem and pursues "the known options within his or her technical grasp," the resulting discovery "is likely the product not of innovation but of [*14] ordinary skill and common sense." **KSR, 127 S. Ct. at 1742**. So too, "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress." **Id. at 1741**. In other cases, though, researchers can only "vary all parameters or try each of numerous possible choices until one possibly arrive[s] at a successful result, where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988)*. In such cases, "courts should not succumb to hindsight claims of obviousness." *In re Kubin, 561 F.3d 1351, 1359 (Fed. Cir. 2009)*. Similarly, patents are not barred just because it was obvious "to explore a new technology or general approach that seemed to be a promising field of

experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell, 853 F.2d at 903*.

In this case, there is no credible evidence that the structural modification was routine. The district court found that the appellee's [*15] expert was evasive on this topic, stating that the witness "did not directly respond to most questions posed to him about whether it would be common for a chemist who develops a pyridine compound to conceive of and make [2-pyr EHDP, 3-pyr EHDP, and 4-pyr EHDP] isomers." *Procter & Gamble, 536 F. Supp. 2d at 486*. But evidence of evasion is not necessarily evidence that the testimony would otherwise have been favorable. The only direct evidence that the structural modification was routine was presented by an expert witness that the district court judge discredited. [1]

> 1 Appellant's expert testified that "if someone was aware that [2-pyr EHDP] was safe and effective, they would immediately in terms of the drug discovery effort, make the [3-pyr EHDP]." However, the district court concluded that this witness "had no specialized experience in the area of bisphosphonates" aside from his preparation to testify in the litigation. *Procter & Gamble, 536 F. Supp. 2d at 480*. Additionally, the expert prepared his opinion by reviewing drug profiles in the current version of the Physician's Desk Reference instead of drug profiles from the relevant time, causing his opinions to be "marred by hindsight." [*16] *Id. at 495*.

Accordingly, we conclude that the district court did not clearly err in finding that Teva had not established a prima facie case of obviousness as to the challenged claims of the *'122 patent*.

V. Unexpected Results

The district court found that, even if Teva could establish a prima facie case of obviousness, P&G had introduced sufficient evidence of unexpected results to rebut such a showing. Such evidence included "test data showing that the claimed composition[] possess[es] unexpectedly improved properties or properties that the prior art does not have." *In re Dillon, 919 F.2d 688, 692-93 (Fed. Cir. 1990)*. Because Teva did not establish a prima facie case of obviousness, P&G need not rely on this evidence to defend the *'122 patent*.

Nonetheless, we note that P&G's witnesses consistently testified that the properties of risedronate were not expected. For example, Dr. Benedict testified that he and other researchers did not predict the potency of risedronate. Ms. McOsker testified that she was "very surprised" by the low dose at which risedronate was effective. Dr. Miller stated that the superior properties of risedronate were unexpected and could not have been predicted. In [*17] a test to determine the lowest dose at which these compounds caused toxic reactions, risedronate outperformed 2-pyr EHDP by a substantial margin. Risedronate showed no observable toxic effect at a dose of 0.75 mg P/kg/day, while 2-pyr EHDP's "no observable effect level" was only 0.25 mg P/kg/day. In another test involving live animals, 2-pyr EHDP was lethal at a dose of 1.0 mg P/kg/day while risedronate was not. Ultimately, the district court weighed the evidence and evaluated the credibility of the witnesses in concluding that P&G had introduced sufficient evidence of unexpected results to rebut any finding of obviousness.

VI. Secondary Considerations of Non-Obviousness

[HN12] Secondary considerations of non-obviousness include the commercial success of the invention at issue and its satisfaction of a long-felt need. *B.F. Goodrich Co. v. Aircraft Braking Sys. Corp., 72 F.3d 1577, 1582 (Fed. Cir. 1996).* The district court found that secondary considerations supported a finding of non-obviousness. When present, such factors "may often be the most probative and cogent evidence [of non-obviousness] in the record." *Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538 (Fed. Cir. 1983).*

The district [*18] court found that risedronate, marketed as Actonel, has been an undisputed commercial success and satisfied a long-felt unmet need. 2 This conclusion was based on the testimony of Dr. Daniel C. Smith, who stated that risedronate experienced favorable growth and had amassed $ 2.7 billion in aggregate domestic sales. The district court based its finding of a long-felt unmet need on the fact that, in the mid-1980s, osteoporosis was recognized as a serious disease and existing treatments were inadequate. However, because the competing drug alendronate was available before risedronate, Teva contends that risedronate could not have satisfied any unmet need. Teva argues that the long-felt need must be unmet at the time the invention becomes available on the market, when it can actually satisfy that need. To support this argument, Teva cites

Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877 (Fed. Cir. 1998). In fact, *Monarch* rejects a similar argument partly because the competing inventions were not actually produced until after the claimed invention's filing date. *Id. at 884.* Here, alendronate was not produced until ten years after the filing of the *'122 patent.* Under *Monarch,* [*19] we look to the filing date of the challenged invention to assess the presence of a long-felt and unmet need. Accordingly, it was not clear error for the district court to conclude that risedronate met such a need and that secondary considerations supported a finding of non-obviousness.

2 The court rightly gave little weight to risedronate's commercial success because the prior art *'406 patent* was also assigned to P&G. As of December 6, 1985, the filing date of the *'122 patent,* 2-pyr EHDP could be found only in a pending application for the *'406 patent,* which was not available to the public. *See Merck & Co., Inc. v. Teva Pharms. USA, Inc., 395 F.3d 1364, 1377 (Fed. Cir. 2005)* (holding that commercial success is not significantly probative of non-obviousness where others are barred from acting on the prior art).

VII. Whether the *'406 Patent* is Prior Art

As an alternative to its position that risedronate was not obvious, P&G argues that the *'406 patent* should not be considered prior art with respect to the *'122 patent* because risedronate was first synthesized by P&G before the *'406 patent* was filed. At trial, Dr. Benedict, one of the inventors named in the *'122 patent,* testified that he synthesized [*20] risedronate in May 1985. P&G submitted a portion of Dr. Benedict's laboratory notebook which contains a May 3, 1985 entry detailing the structure of risedronate and the procedure for its synthesis, but this entry was unwitnessed and was not corroborated by any other evidence.

[HN13] "It is well established that when a party seeks to prove conception via the oral testimony of a putative inventor, the party must proffer evidence corroborating that testimony." *Shu-Hui Chen v. Bouchard, 347 F.3d 1299, 1309 (Fed. Cir. 2003).* The inventor "must provide independent corroborating evidence in addition to his own statements and documents." *Hahn v. Wong, 892 F.2d 1028, 1032 (Fed. Cir. 1989).* Because P&G did not provide adequate corroborating evidence of an earlier invention date for

risedronate, the district court correctly concluded that the *'406 patent* qualifies as prior art for purposes of this inquiry.

VIII. Obviousness-Type Double Patenting

In addition to its obviousness defense, Teva also asserted that the *'122 patent* was invalid for double patenting. [HN14] The double patenting doctrine is designed to prevent a patent owner from extending his exclusive rights to an invention through claims in a later-filed [*21] patent that are not patentably distinct from claims in the earlier filed patent. *Geneva Pharms., Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 1378 (Fed. Cir. 2003.)* In general, the obviousness analysis applies to double patenting, except for three distinctions. First, statutory obviousness compares claimed subject matter to the prior art, while non-statutory double patenting compares claims in an earlier patent to claims in a later patent or application. *Id. at 1377 n.1.* Second, double patenting does not require inquiry into a motivation to modify the prior art. *Id.* Finally, double patenting does not require inquiry into objective criteria suggesting non-obviousness. *Id.*

Having concluded that risedronate was not obvious under *35 U.S.C. § 103*, we similarly conclude that the *'122 patent* is not invalid for obviousness-type double patenting. Additionally, we agree with the district court that the claims of the *'122 patent* are distinct from the claims of the *'406 patent*. Comparing the claims of the *'122 patent* to those of the *'406 patent*, we note that, while claims 4 and 16 of the *'122 patent* explicitly claim the risedronate compound, the *'406 patent* claims an intermittent dosing regimen for [*22] the treatment of osteoporosis and claims no new compounds. Accordingly, Teva failed to present clear and convincing evidence of overlap between the claims of the two patents to invalidate the *'122 patent* based on obviousness-type double patenting.

III. CONCLUSION

For the foregoing reasons, we affirm.

AFFIRMED